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14. ABSTRACT
The most human of emotions are defined by how we feel about others. Such other-regarding preferences (ORP), in the parlance of economics, both permit and necessitate the institutions that form the core of modern society. Abnormal functionalities associated with ORP in the brain are also thought to be a critical component underlying neuropsychiatric disorders marked by social deficits. The primary objectives of the research project are to develop an animal model of ORP (Objective 1), and investigate the functional contributions of the brain circuits (Objectives 2-3) and neuropeptide oxytocin (OT) (Objective 4). We have successfully developed a rhesus macaque model of ORP and demonstrated that rhesus monkeys care about rewards delivered to another monkey (Chang et al., 2011). We then for the first time demonstrated that inhaled OT using a pediatric nebulizer effectively reaches the central nervous system of rhesus macaques, providing a proof of concept for a clinical OT treatment method well-tolerated by children. Subsequently, we showed the inhaled OT promotes prosocial preferences and social gaze rates (Chang et al., 2012). Furthermore, we have recorded single neuron activity from OFC as well as the anterior cingulate sulcus (ACCs) and gyrus (ACCg) during the ORP task (Chang and Platt, 2013). Finally, we have inactivated OFC and ACCg and found differential causal contribution to social behaviors between these brain regions. Our results begin to elucidate neural mechanisms underlying ORP and open up future research aimed at understanding how therapeutic OT treatments in individuals with autism spectrum disorders work in their brains.

15. SUBJECT TERMS
social decision-making; oxytocin; vicarious reinforcement; rhesus macaques; the orbitofrontal cortex; social preference; autism spectrum disorders; prosocial behavior; other-regarding preference; social gaze

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INTRODUCTION

Autism spectrum disorders (ASD) differ from other developmental disorders in that children with ASD show little interest in other people (Kanner 1943). This lack of interest is associated with other complex social deficits, including empathy and shared attention, thus further disrupting the capacity to engage in normal social interactions (Batson et al 1981; Goldman 1993). Research findings suggest that social problems in ASD derive, in part, from dysfunction in the neural circuits that motivate the other-regarding behaviors that shape normal social interactions (Bowles 2006; Nichols 2001). Other-regarding preferences (ORPs) describe a concern for the welfare or the benefit of others (Dufwenberg et al 2008; Fehr & Fischbacher 2003). ORPs may rely on empathy, a social-cognitive capacity severely compromised in ASD (Baron-Cohen et al 1985), and pathological deficits of empathy in ASD may result from a failure to understand others' internal states (Baron-Cohen et al 1985). Accumulating evidence implicates orbitofrontal cortex (OFC) and medial frontal cortex, including the anterior cingulate gyrus (ACCg), dysfunction in the pathophysiology of ASD (Bachevalier & Loveland 2006; Girgis et al 2007; Gilbert et al., 2009). Furthermore, oxytocin (OT), a neuromodulatory hormone implicated in social behavior in mammals, has also been implicated in the etiology of ASD. Understanding the neuronal properties of prefrontal cortical neurons and demonstrating OT-induced changes in ORP in a rhesus macaque model will significantly advance our understanding of social processing in both healthy and ASD brains. Our research aims to develop a non-human primate model for ORP specifically designed to probe these mechanisms in healthy individuals, the neuronal mechanisms involved in the expression of ORPs, and the efficacy of pharmacological OT therapies designed to enhance social interaction in ASD.

BODY

Objectives specified in the approved Project Narratives

Our objectives remain unchanged from the last report.

- Objective 1: Develop an animal model of ORPs.
- Objective 2: Determine how OFC neurons mediate ORPs.
- Objective 3: Determine the effects of OFC perturbations on ORPs.
- Objective 4: Determine whether OT can enhance positive ORP.

By tasks indicated in Statements of Work (SOW)

Task 1. Characterize neural responses in the orbitofrontal cortex (OFC)

We have completed this task. We first developed an other-regarding preference (ORP) task in pairs of rhesus macaques. We found that actor monkeys prefer cues paired with reward to a recipient monkey over cues paired with reward to no one, displaying prosocial preference. By contrast, in a different decision context, the actors prefer cues paired with reward to self over cues paired with reward to both monkeys simultaneously, displaying antisocial preference. Rates of attention to M2 strongly predicted the strength and valence of vicarious reinforcement. These patterns of behavior, which were absent in non-social control trials, are consistent with vicarious reinforcement based upon sensitivity to the rewarding experiences of another individual. Vicarious reward may play a critical role in shaping cooperation and competition, as well as motivating observational learning and group coordination in rhesus macaques, much as it does in humans. **The detailed methods, results, and figures for the ORP task can be found in the Appendix 1 and were published in Frontiers in Decision Neurosciences in 2011 (Chang et al., 2011).**

We next recorded the activity of 85 single orbitofrontal (OFC) neurons, 101 single anterior cingulate sulcus (ACCs) neurons, and 81 anterior cingulate gyrus (ACCg) neurons from two donor monkeys performing the ORP task. We found that OFC neurons encode rewards that are delivered to oneself, whereas ACCg neurons encode reward allocations to the other monkey, to oneself or to both. ACCs neurons, on the other hand, signaled reward allocations to the other monkey or to no one. In this network of received (OFC) and foregone (ACCs) reward signaling, ACCg emerged as an important nexus for the computation of shared experience and social reward. **The detailed methods, results, and figures for the neuronal results can be found in the Appendix 2 and were published in Nature Neurosciences in 2013 (Chang et al., 2013)**

Task 2. Characterize behavior after muscimol inactivation of prefrontal cortex

We are close to completing the task. Our neuronal recording results strongly indicate that the ACCg, rather than OFC, is most critical for social representation and social learning (Chang et al., 2013). Therefore, we tested the causality of ACCg neurons in addition to neurons in a series of prefrontal areas in social versus non-social processing. In order to be more time efficient as well as to generalize the finding across different behavioral paradigms, we in parallel trained new monkeys to perform observational social

learning tasks, which also depend on sensitivity to the rewarding experiences of another individual. We tested the causal contribution of ACCg and insula to social learning by investigating whether observer monkeys could learn the value of a novel food by observing the behavior of a demonstrator monkey tasting the food. We tested social learning following muscimol inactivation of the neuronal populations in ACCg, in which we found social encoding of donated and shared rewards, and in the insula, known to be involved in direct experience learning, especially with disgust learning, compared with saline control injections. The insula is known to be hypoactive in ASD (Uddin and Menon, 2009).

We hypothesize that ACCg is an essential node of the neural network mediating the acquisition of positive and negative food preferences through social learning (**Figure 1**), consistent with the finding that ACCg neurons encode the rewarding experiences of another individual (Chang et al., 2013). By contrast, we hypothesize that the insula is only involved in non-social learning through direct experience. ACCg has been implicated in empathy and social learning in humans. We previously showed that neurons in ACCg respond when monkeys choose to give juice to another monkey while neurons in OFC respond when monkeys choose to give juice to themselves (Chang et al., 2013). Damage to ACCg, but not OFC, causes disruptions in social behavior in monkeys (Rudebeck et al., 2009).

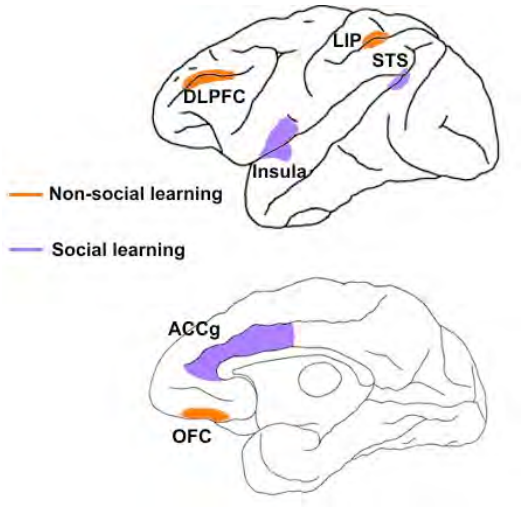

Figure 1. Brain areas involved in social and nonsocial learning. Based on Chang et al., 2013, we hypothesize that ACCg is causally involved in social learning, whereas the insula is causally involved in non-social learning through direct experience.

In these experiments, one monkey, the demonstrator, sits in a primate chair and eats food offered to him. Another monkey, the actor, observes the demonstrator. The foods offered are colored “pearls” made from gelatin and either “good” (citrus or berry; sweet) or “bad” (quinine; bitter) flavoring. Each of the two types of pearl used per session is assigned a distinctive color (e.g. green good pearls and blue bad pearls), which changes each session. Sessions alternate between demonstration sessions and test sessions. In demonstration sessions, the demonstrator is given the opportunity to eat 10 good pearls and 10 bad pearls, one at a time, in random order. In pilot studies, after sampling a good pearl the demonstrator monkey consumes it and then reaches quickly for another when it is offered; after sampling a bad pearl, the demonstrator monkey displays a distasteful facial expression, spits out the pearl, and rejects bad pearls on subsequent trials by throwing them away. Observer monkeys subsequently direct their gaze to palatable foods and display tongue protrusion and licking. By measuring visual orienting and tongue protrusion while presenting the good and bad pearls, we assess learning of food preferences without giving subjects direct access to food. These data are then compared with food preferences subjects develop when permitted to directly sample pearls. After observer monkeys display preferences for the good foods learned from social observation and through direct experience, we invert the flavor/color associations. We found that observer monkeys typically relearned the novel food values within the first session.

We have systematically explored the neural circuitry necessary for social learning by inactivating these neuronal populations using the GABA agonist muscimol. Our preliminary data (**Figure 2**) show that reversible pharmacological inactivation of ACCg severely impairs social learning (baseline good food: 2.41 ± 0.36 vs bad: 1.35 ± 0.30 seconds spent looking at food; after muscimol injection, good: 1.54 ± 0.35 vs bad: 2.44 ± 0.41; t-test, both $p < 0.05$). However, non-social learning from direct experience was not blocked (baseline good: 2.92 ± 0.50 vs bad: 1.76 ± 0.37 seconds spent looking at food; after the muscimol injection, good: 1.91 ± 0.38 vs bad: 1.23 ± 0.23; t-test, both $p < 0.05$). These results come from 12 injections in two monkeys By contrast, we found the opposite patterns in insula – inactivating insula neurons impaired learning from direct experience (baseline good: 2.11 ± 0.10 vs bad: 0.99 ± 0.05 seconds spent looking at food; after the muscimol injection, good: 0.45 ± 0.04 vs bad: 1.02 ± 0.05; t-test, $p < 0.05$ for both). However, social learning was intact (baseline good: 2.16 ± 0.10 vs bad: 1.26 ± 0.07 seconds spent looking at food; after the muscimol injection, good: 1.01 ± 0.05 vs bad: 0.52 ± 0.04; t-test, $p < 0.05$ for both). These results come from 8 injections of muscimol in two monkeys. These results provide causal evidence that ACCg is specialized for incorporating the experience of another individual into one's own behavior, a form of empathy, whereas insula contributes to behavior modified by direct experience. We are currently analyzing whether muscimol inactivation of ACCg and insula differentially influence social attention during social and non-social learning. A manuscript based on this work is currently in preparation (Gariépy et al., in prep).

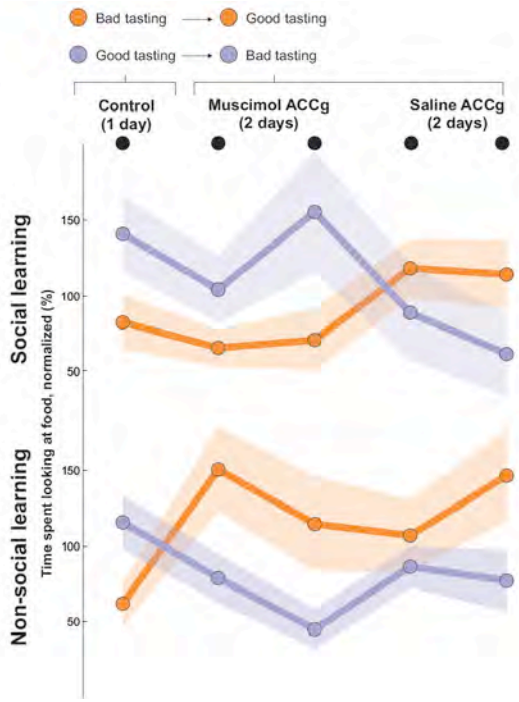

Figure 2. Muscimol injections into ACCg impaired social learning (top curves) but not direct learning (bottom curves) of food palatability.

We are currently testing the causal contributions in OFC neuronal populations to compare the results directly across ACCg, OFC, and the insula for their roles in social and experience-based learning.

Task 3. Determine behavioral response to microstimulation

We have not yet begun this task.

Task 4. Examine the effect of oxytocin (OT) on task performance

We have completed this task. We showed, for the first time in a monkey or a human, that inhaling OT (using pediatric nebulizer) penetrates the central nervous system and subsequently enhances the sensitivity of rhesus macaques to rewards occurring to others as well as themselves in the ORP task. Roughly 2 hours after inhaling OT, donor

monkeys increased the frequency of prosocial choices associated with reward to another monkey (i.e., recipient monkey) when the alternative was to reward no one. OT also increased attention to the recipient monkey as well as the time it took to make such a decision. In contrast, within the first 2 hours following inhalation, OT enhanced selfish choices associated with delivery of reward to self over a reward to the other monkey, without influencing attention or decision reaction times. Thus, inhaling OT causally promotes prosocial behavior in rhesus monkeys when there is no perceived cost to self. These findings potentially validate the use of inhaled OT as a potential therapeutic for enhancing social attention and prosocial behavior in ASD. This study also pioneered the use of a pediatric nebulizer to deliver OT to the brain, a method that may be well-tolerated by children. **The detailed methods, results, and figures can be found in the Appendix 3 and were published in Proceedings of the National Academy of Sciences in 2012 (Chang et al., 2012).**

KEY RESEARCH ACCOMPLISHMENTS [see REPORTABLE OUTCOMES]

- Demonstrated that rhesus monkeys are sensitive to the experiences of others in the reward donation task (Presented at multiple meetings, Paper Published: Chang et al., 2011)

- Development of intranasal oxytocin (OT) protocol in rhesus monkeys with a confirmation that the method effectively delivers OT to the central nervous system (Meeting Presentations, Paper Published: Chang et al., 2012). Now this method is the standard in the field for delivering OT to nonhuman primates, and is being investigated for use in children.

- Demonstrated that OT enhances prosocial behavior and social attention in rhesus monkeys (Presented at multiple meetings) (Meeting Presentations, Paper Published: Chang et al., 2012)

- Discovered that the orbitofrontal cortex (OFC) does not play a critical role in processing information about the experiences of others, a basic component of empathy (Meeting Presentations, Paper Published: Chang et al., 2013)

- Discovered that the anterior cingulate gyrus (ACCg) plays a critical role in processing information about the experience of others, a basic component of empathy (Meeting Presentations, Paper Published: Chang et al., 2013)

- Extension of the current experiments to other prefrontal brain regions (the sulcus and gyrus of the anterior cingulate cortex) to better understand how ORP-related signals differ across different parts of the prefrontal cortex (Meeting Presentations, Paper Published: Chang et al., 2013)

- Extension of the reward donation findings to social learning to generalize how ACCg, OFC, and the insula contribute to social behavior (Meeting Presentations, Paper Published: Chang et al., 2013)

- Demonstration that ACCg contributes causally to social learning and the insula contributes to learning from direct gustatory experience (Meeting Presentations, Paper in prep: Gariépy et al.)

REPORTABLE OUTCOMES

A. Publications

1. Gariépy JF, Chang SWC, Du E, Erb J, Platt ML (*in revision*) Neuronal basis of deceptive behaviour in rhesus macaques. *Nature Neurosc*.

2. Gariépy JF, Watson KK, Du E, Xie DL, Erb J, Amasino D, Platt ML (2013, in revision) Social learning in humans and other animals. *Frontiers in Decision Neuroscience*.

3. Gariépy JF, Du E, Xie DL, Platt ML (*in prep*) Neural basis of social learning in macaques.

4. Chang SW and Platt ML (*in revision*) Oxytocin and social cognition in rhesus macaques: Implications for understanding and treating human psychopathology. *Brain Research: Special Issue in Oxytocin and Social Behavior*.

5. Chang SW, Gariépy JF, and Platt ML (2013) Neuronal reference frames for social decisions in primate prefrontal cortex. *Nat. Neurosci.*, 16, 243-250.

6. Gariépy JF, Chang SW and Platt ML (2013) Brain games: Toward a neuroecology of social behavior. Invited commentary in *Beh. Brain. Sci.*, 36, 424-5.

7. Chang SW, Barack DL and Platt ML (2012) Mechanistic classification of neural circuit dysfunctions: Insights from neuroeconomics research in animals. *Biol. Psychiatry*, 72:101–106.

8. Chang SW, Barter JW, Ebitz RB, Watson KK and Platt ML (2012) Inhaled oxytocin amplifies both vicarious reinforcement and self reinforcement in rhesus macaques (*Macaca mulatta*). *Proc Natl Acad Sci*, 109, 959–964.

9. Chang SW, Winecoff AA, and Platt ML (2011) Vicarious reinforcement in rhesus macaques (*Macaca mulatta). Front. Neurosci.*, 5, 27.

B. Meeting Abstracts

1. Gariépy JF. Prefrontal contributions to social Learning and decision-making in rhesus macaques. *Neural circuits for adaptive control of behavior (Paris, France), 2013 (Talk)*

2. Gariépy JF, Chang SW, Du E, Platt ML. Neural basis of deceptive tactics in the primate prefrontal cortex. *The Assembly and Function of Neural Circuits (Monte Verita, Switzerland) 2013 (Poster)*

3. Gariépy JF, Du E, Xie D, and Platt ML. Neural basis of social learning in rhesus macaques. *Society for Neuroscience (San Diego, CA), 2013 (Poster)*

4. Xie D, Gariépy JF, Du E, and Platt ML. Inhaling oxytocin increases contagious yawning in rhesus macaques. *Society for Neuroscience (San Diego, CA), 2013 (Poster)*

5. Chang SW, Gariépy JF, and Platt ML. Differential encoding of social decision outcomes by neurons in primate orbitofrontal cortex, dorsal anterior cingulate cortex and anterior cingulate gyrus. *Society for Neuroscience (New Orleans, LA), 2012 (Talk) & Contributed Talk at Society for Social Neuroscience, 2012*

6. Gariépy JF, Chang SW, Du E. and Platt ML. Neural correlates of deceptive tactics in the primate prefrontal cortex. *Society for Neuroscience (New Orleans, LA), 2012 (Talk) (also for Society for Social Neuroscience)*

7. Chang SW, Gariépy JF, and Platt ML. Neuronal reference frames for social decisions in primate prefrontal cortex. *Organization for Computational Neuroscience (Atlanta, GA), 2012 (Poster)*

8. Platt, ML. Neuronal basis of giving and receiving. *Organization for Computational Neuroscience (Atlanta, GA), 2012, invited talk.*

9. Gariépy JF, Chang SW, Du E. and Platt ML. Neural correlates of deceptive tactics in the primate prefrontal cortex. *Tenth International Congress of Neuroethology, 2012 (Poster)*

10. Chang SW and Platt ML. Differential coding of egocentric and allocentric reward outcomes during social interaction in primate ACC and OFC. *Society for Neuroscience (Washington, DC), 2011 (Talk)*

11. Chang SW, Barter JW, Ebitz RB, Watson KK and Platt ML. Oxytocin promotes prosocial decisions in rhesus macaques. *Society for Neuroscience (Washington, DC), 2011 (Poster)*

12. Chang SW, Barter JW, Ebitz RB, Watson KK and Platt ML. Inhaled oxytocin amplifies both vicarious reinforcement and self reinforcement in rhesus macaques *(Macaca mulatta).* Workshop on the Biology of Prosocial Behavior at Emory University *(Atlanta, GA), 2011 (Poster)*

13. Chang SW and Platt ML. Social Context Gates Other-Regarding Preferences in Rhesus Macaques (*Macaca mulatta*). *Society for Neuroscience (San Diego, CA), 2010 (Poster)*

14. Chang SW and Platt ML. Social Context Gates Other-Regarding Preferences in Rhesus Macaques (*Macaca mulatta*). A Brain Research meeting: The *Emerging Neuroscience of Autism Spectrum Disorders (San Diego, CA), 2010 (Poster)*

C. Research Support (built upon this award)

1. NIH/NIMH 2/21/12 - 11/30/16
   R01 MH095894-01 (*Platt*)
   Neuronal basis of vicarious reinforcement dysfunction in autism spectrum disorder
   The goal of this project is to understand the role of prefrontal cortex in mediating vicarious reinforcement during reward allocation decisions

2. Duke Department of Neurobiology 6/01/11 – 5/31/12
   Postdoctoral Training Award in Fundamental & Translational Neuroscience
   NIH/NINDS T32 NS051156-07 (*Chang*)
   Neural basis of other-regarding preference
   The goal of this project is to understand the role of anterior cingulate cortex and orbitofrontal cortex during reward allocation decisions

3. NIH/NIMH 9/01/12 – 8/31/17
   NIH K99/R00 Pathway to Independence (*Chang*)
   Role of oxytocin in the amygdala-prefrontal network during social decision-making
   The goal of this project is to undergo extensive training in neuroendocrinology, and study the mechanisms underlying oxytocin-mediated neural processing across amygdala and prefrontal neurons in social decision-making.

4. FRQS 9/01/12 – 9/01/15
   25559 Post-doctoral award (Gariépy)
   Neural basis of social behaviors in rhesus macaques.
   The goal of this project is to identify the regions of the prefrontal cortex necessary for learning of food quality by direct experience and by social observation.

D. Mentoring

1. A successful rotation project for a Duke Cognitive Neuroscience PhD candidate, Amy A. Winecoff, resulting in a second authorship in Chang et al., 2011.
2. A successful rotation project for a Duke Cognitive Neuroscience PhD candidate, Joseph W. Barter, resulting in a second authorship in Chang et al., 2012.
3. A successful launch of many related projects by Dr. Jean-Francois Gariépy
4. A successful rotation project for a Duke Cognitive Neuroscience PhD candidate, Amanda V. Utevsky.
5. A successful transition to a faculty position for Dr. Steve Chang (Yale Univ.)
6. Successful mentoring of Emily Du and Diana L. Xie (Duke University) and Joshua Erb (Columbia University) as undergraduate interns who have worked on these projects.

CONCLUSION

Other-regarding preferences (ORPs) are critical for normal social behavior, and the neural mechanisms underlying ORPs may be disrupted in neuropsychiatric disorders marked by social deficits, including autism spectrum disorders (ASD). Both reward-related processing in the brain and the neuropeptide oxytocin (OT) have been implicated in ASD. However, the neural mechanisms underlying ORPs remain elusive, partly due to the lack of a good animal model for studying complex social behavior. To address this gap, we developed a novel social interaction task involving two rhesus macaques, and investigated the role of prefrontal cortical neurons, previously implicated in motivation and decision-making, as well as the neuropeptide OT, which has previously been implicated in social preferences, during the expression of ORPs.

We found that rhesus monkeys care about what happens to others, as indicated by their preference to deliver juice rewards to a recipient monkey over no one and increased attention to the recipient monkey following prosocial decisions. Inhalation of OT by monkeys increases both the frequency of prosocial decisions and attention to the recipient monkey. Neuronal recording from OFC revealed that OFC neurons track directly experienced rewards during social interactions. By contrast, ACCg neurons signaled rewards delivered to another individual as well as shared rewards. Further testing revealed that ACCg is specialized for social learning, whereas the insula is not but rather serves learning from direct experience. Our studies thus have begun to reveal how the primate brain makes decisions during social interaction with other individuals.

OT has been evaluated for potential therapeutic use in clinical conditions marked by social deficits, such as ASD, antisocial personality disorder, and schizophrenia. Notably, the nebulization method we developed demonstrated that inhaled OT actually translocates to the central nervous system. Moreover, nebulization is well-tolerated by children for delivery of other therapeutics (e.g., albuterol), thus opening up avenues for early OT intervention in childhood.

Our findings provide new opportunities for uncovering the neurophysiological and neuroendocrinological mechanisms underlying complex social behavior in a species much more closely related to humans than mice or rats. Rhesus monkeys have long served as the preferred model species for probing the neural mechanisms underlying complex cognition. Given the strong similarities in social behavior and cognition, together with remarkable homologies in neural circuitry, the rhesus macaque provides a powerful model for probing the neurobiological mechanisms of social interactions in people.

Medical Implications (“So What” section)

Our work holds promise both for understanding the basic mechanisms that support complex social behavior and translating that knowledge into improved treatment for social dysfunction in ASD. In particular, our work tests the idea that empathy derives from the activation of neural circuits that process primary emotions or feelings, such as reward or punishment, merely by observing the same things happen to other people. OT therapy for ASD and other neuropsychiatric disorders is currently being explored in clinical trials,

despite uncertainty regarding the exact mechanism of action in the brain or the long-term consequences of use. By testing this drug in an animal model, we can directly confirm efficacy, efficiency, and long-term safety. Clinicians can use this information to directly inform therapeutic interventions in ASD. We demonstrated, for the first time in any species, that inhaled OT is taken up by the central nervous system—an important prerequisite for exploring further clinical opportunities.

Our work promises ancillary benefits as well. Our findings regarding the functional role of the OFC, ACCg, and now the insula will also be of use in clinical contexts. The precise way that prefrontal cortical circuits contribute to social behavior remains poorly understood. Our studies have begun to sketch out how these circuits mediate social behavior. Our findings may prove invaluable in the diagnosis and treatment of social behavioral disorders that accompany head trauma, with potentially important implications for veterans of US armed forces returning from the battlefield suffering from traumatic brain injuries and attendant problems in adjusting to civilian life.

Ultimately, the results of our studies will inform therapeutic interventions for social disorders, on both the pharmacological and behavioral levels, and significantly improve the lives of people living with ASD and other individuals struggling with social life.

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APPENDICES

Appendix 1

Chang SW, Winecoff AA, and Platt ML (2011a) Vicarious reinforcement in rhesus macaques (*Macaca mulatta*). *Front. Neurosci.*, 5, 27.

Appendix 2

Chang, SW, Gariépy, JF, & Platt, ML (2013) Neuronal reference frames for social decisions in primate frontal cortex. *Nature Neurosci.,* 16, 243-250.

Appendix 3

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Vicarious reinforcement in rhesus macaques (*Macaca mulatta*)

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What happens to others profoundly influences our own behavior. Such other-regarding outcomes can drive observational learning, as well as motivate cooperation, charity, empathy, and even spite. Vicarious reinforcement may serve as one of the critical mechanisms mediating the influence of other-regarding outcomes on behavior and decision-making in groups. Here we show that rhesus macaques spontaneously derive vicarious reinforcement from observing rewards given to another monkey, and that this reinforcement can motivate them to subsequently deliver or withhold rewards from the other animal. We exploited Pavlovian and instrumental conditioning to associate rewards to self (M1) and/or rewards to another monkey (M2) with visual cues. M1s made more errors in the instrumental trials when cues predicted reward to M2 compared to when cues predicted reward to M1, but made even more errors when cues predicted reward to no one. In subsequent preference tests between pairs of conditioned cues, M1s preferred cues paired with reward to M2 over cues paired with reward to no one. By contrast, M1s preferred cues paired with reward to self over cues paired with reward to both monkeys simultaneously. Rates of attention to M2 strongly predicted the strength and valence of vicarious reinforcement. These patterns of behavior, which were absent in non-social control trials, are consistent with vicarious reinforcement based upon sensitivity to observed, or counterfactual, outcomes with respect to another individual. Vicarious reward may play a critical role in shaping cooperation and competition, as well as motivating observational learning and group coordination in rhesus macaques, much as it does in humans. We propose that vicarious reinforcement signals mediate these behaviors via homologous neural circuits involved in reinforcement learning and decision-making.

Keywords: vicarious reinforcement, social reward, gaze, social interaction, rhesus macaques

INTRODUCTION

Reinforcement learning provides a powerful mechanism for associating stimuli and actions with the direct experience of reward and punishment (Rescorla and Wagner, 1972; Schultz et al., 1997; Sutton and Barto, 1998). Behavioral and neurobiological evidence indicate that human behavior also depends on outcomes that have not been directly experienced. For example, fictive, or counterfactual, learning describes sensitivity to reward outcomes for options that were not chosen, were merely observed, or were even imagined (Byrne, 2002; Lohrenz et al., 2007; Epstude and Roese, 2008). Fictive learning can be described formally in terms analogous to reinforcement learning (Lohrenz et al., 2007), and may depend on overlapping neural circuitry (Lohrenz et al., 2007; Hayden et al., 2009; Mobbs et al., 2009).

Observing what happens to others also powerfully shapes human learning and behavior (Berger, 1962; Bandura and McDonald, 1963; Bandura et al., 1963). Such other-regarding outcomes can drive observational learning (Mobbs et al., 2009; Jeon et al., 2010), and motivate other-regarding behaviors such as cooperation and charity, as well as spite and schadenfreude (Takahashi et al., 2009). The "warm glow" hypothesis (Andreoni, 1990) suggests that vicarious reward and punishment motivates individuals to prefer either positive or negative outcomes to others (Bandura et al., 1963; Fehr and Fischbacher, 2003; Mobbs et al., 2009). Human social emotions associated with vicarious reward and punishment, such as fairness and envy, appear early in ontogeny, and their derangement in mental disorders like psychopathy can have devastating consequences (Kiehl, 2006).

Such observations endorse the idea that neural mechanisms supporting vicarious reinforcement are derived specializations of the human brain, which support complex social behavior including observational learning, cooperation, and even altruism (Fehr and Fischbacher, 2003). Though highly specialized for complex social behavior in humans, these mechanisms appear to have deep evolutionary roots. Behavioral and neurobiological evidence demonstrate rudimentary forms of fictive, observational, and social learning in non-human animals. Rhesus macaques, for example, learn from fictive outcomes and this process appears to be supported by the same circuitry mediating fictive learning in humans (Hayden et al., 2009). In some species, learning to perform a task is facilitated by watching others learn the same task (Zentall and Levine, 1972; Zentall et al., 1996; Drea and Wallen, 1999; Subiaul et al., 2004; Whiten et al., 2009). Chimpanzees are capable of learning to use complex tools by observing others (Tomasello et al.,

1987), and their observational learning seems to be contingent on the associative strength of observed action and outcome (Crawford and Spence, 1921). Observing another mouse receive a shock can drive fear conditioning in the observer, and this observational fear conditioning depends on affective pain circuitry that has been implicated in empathy in humans (Jeon et al., 2010).

Whether mere observation of rewarding events occurring to another individual can drive the expression of social preferences in non-human animals, as proposed by the "warm glow" model, however, remains debated. Some have argued that the expression of other-regarding preferences in humans reflects the evolution of mechanisms that promote cooperative reproduction, but the evidence for other-regarding behaviors in cooperatively breeding animals remains controversial (Burkart et al., 2007; de Waal et al., 2008; Lakshminarayanan and Santos, 2008; Massen et al., 2010). Others have argued that only those species most closely related to humans, namely chimpanzees and bonobos, possess the derived features of human biology and cognition, in particular "theory of mind" (Call and Tomasello, 2008), express other-regarding preferences, but again the evidence for such behavior in apes remains inconclusive (Tomasello et al., 2003; Silk et al., 2005).

We hypothesize instead that cooperation and competition endemic to group life favors the evolution of neural circuits tuned to extract information about the experiences of others, and that these circuits serve as the core building blocks for the development of observational learning and other-regarding behaviors, which reach their fullest expression in our own species. As a first behavioral test of this idea, we probed the impact of vicarious reinforcement on subsequent decisions made by rhesus macaques with respect to other monkeys. Rhesus monkeys observe others to gather social information (Cheney and Seyfarth, 1990), display sensitivity to fictive outcomes in non-social settings (Hayden et al., 2009), show rudimentary understanding of the intentions of others (Flombaum and Santos, 2005), care for kin (Maestripieri, 1994), and may give up foods to alleviate pain in conspecifics (Masserman et al., 1964). We hypothesized that such behaviors, as well as naturally occurring behaviors such as social grooming, alliance formation, and group territorial defense, derive from fundamental vicarious reinforcement mechanisms similar to those guiding social behavior in humans.

To test this hypothesis, we capitalized on simple Pavlovian and instrumental conditioning to associate liquid rewards to self and rewards to another monkey with a set of visual cues, and subsequently tested for preferences amongst these cues in a two alternative-forced choice task to infer underlying reward associations. Subsequent preference tests between cues revealed a preference to reward the other monkey rather than no one, but a preference to withhold reward from the other when choosing between rewarding self or both monkeys simultaneously. Crucially, monkeys showed no preferences amongst the cues when the other monkey was removed from the room and replaced with a juice collection bottle, confirming the social dependence of vicarious reinforcement and thus ruling out simple fictive learning as an explanation for the observed behavior. Preferences amongst cues were predicted by the relative subjective value of each cue, as inferred from the time it took to initiate choosing each option, as well as the frequency with which the actor monkey looked at the recipient monkey following choices. These findings demonstrate context-dependent, vicarious reinforcement guides decision-making with respect to others in rhesus macaques.

MATERIALS AND METHODS

GENERAL PROCEDURES

All procedures were approved by the Duke University Institutional Animal Care and Use Committee and were designed and conducted in compliance with the Public Health Service's Guide for the Care and Use of Animals. All rhesus macaques (*Macaca mulatta*) used in the study were genetically unrelated, middle-ranked males (mean age and SD, 9 ± 3.7), and none of M1–M2 pairs were cagemates. All monkeys involved in this study received at least 20 ml/kg of liquid daily in addition to fluid earned in the experiment.

Horizontal and vertical eye positions were sampled (1000 Hz) by an infrared eye-monitoring camera system (SR Research Eyelink). Stimuli were controlled by a computer running Matlab using PsychToolbox (Brainard, 1997; Pelli, 1997). All experiments were carried out in a dimly lit room to ensure visibility of M1 and M2. Both M1 and M2 were head-restrained during the experiments. M2 was always situated diagonally across from M1 at a 45° eccentricity to the right from the center of M1's screen, and they faced each of their own display screens, which were located at a 90° angle from one another (**Figure 1A**). The location of M2 (center of the face) was mapped empirically prior to experiments using M1's eye positions. In the chair/juice control, an empty primate chair with an operating juice tube and a depository bottle replaced M2. The depository bottle was placed in the same space that would otherwise be occupied by M2's mouth region (all else in the control were identical to the M1–M2 condition).

Solenoid valves that delivered the liquid rewards were placed in another room to prevent monkeys from forming secondary associations between solenoid clicks and different reward types. We also included a separate solenoid designated for R_{NONE} that only produced clicks but delivered no fluid. Masking white noise was always played in the experimental room. We used a relatively large juice reward size (0.5–1 ml) per successful trial in order to clearly demonstrate to M1 that M2 received juice rewards on R_{BOTH} and R_{OTHER} trials. The reward size remained constant across different reward conditions within each block. More specifically, the fluid-restricted actor and recipient monkeys received, on average, 250 ml of liquid in the form of cherry juice. The amount of fluid intake across different experimental sessions only fluctuated within ~50 ml. During the days without experimental sessions, the monkeys drank up to 500 ml *ad lib.* or more, which demonstrates the high motivational level. Furthermore, they were very motivated by this reinforcement schedule, given that they participated in the experiments and continued to perform trials for about 2–3 h without stopping.

BEHAVIORAL TASKS AND ANALYSIS

The behaviors from two actor monkeys were examined. The tasks were initially developed for neurophysiological investigations, and therefore we limited the number of the actor monkeys to 2, which is the standard and practical convention for neurophysiological studies. This convention, however, weakens the generalizability of the study. To address this to our best, the current study also reports the main findings and statistics separately for the two monkeys. A

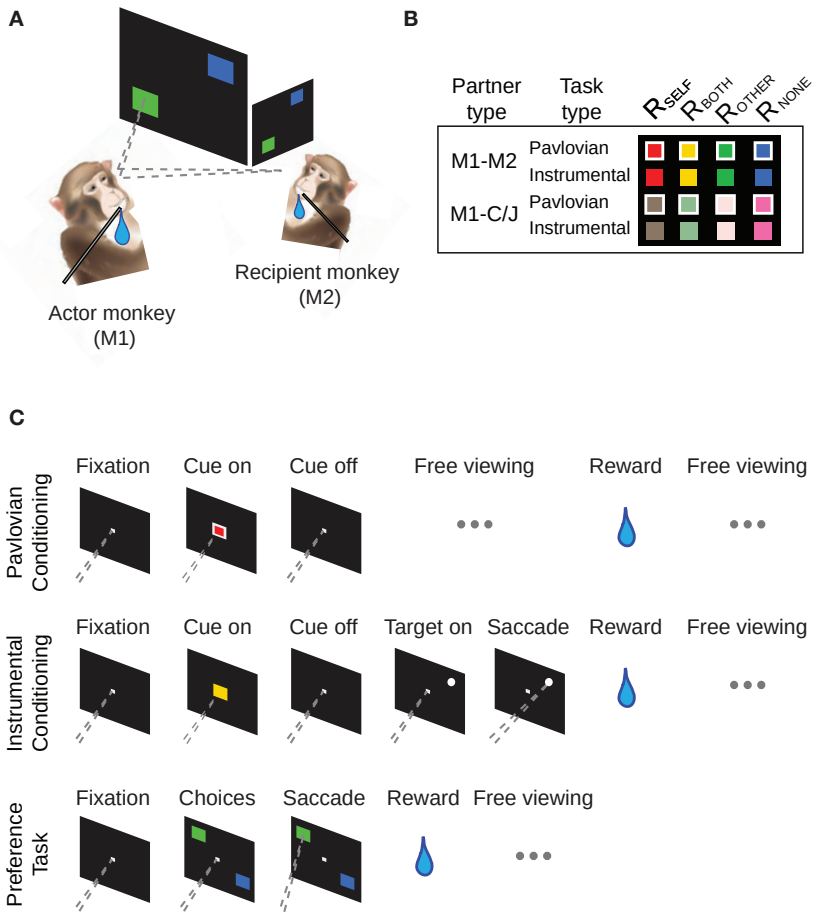

FIGURE 1 | Experimental setup and behavioral paradigms. (A) An actor monkey (M1) performed behavioral tasks in the presence of a recipient monkey (M2) in a dimly lit room. **(B)** Typical stimuli used for the monkey–monkey (M1–M2) and monkey–chair/juice (M1–C/J) conditions. See **Table 1** for all the stimuli used. **(C)** Behavioral tasks. *Top*, Pavlovian conditioning task. *Middle*, instrumental conditioning task. *Bottom*, preference task. Pavlovian and instrumental conditioning trials were randomly interleaved. Preference trials were run to test M1's vicariously conditioned preferences.

total of eight M1–M2 and two M1–chair/juice pairs were used in the study. Of these, three M1–M2 pairs and two chair/juice controls (for each M1) were subjected to both Pavlovian and instrumental conditioning trials with a novel stimulus set for each pair. The remaining five M1–M2 pairs were tested based on already learned cue-reward associations from the conditioning trials (i.e., from the three M1–M2 pairs). The complete set of visual cues used is shown in **Table 1**. One actor monkey (MY) served as M1 first then was also tested as M2 at the very end, whereas the other actor monkey (MO) was tested as M2 at the very beginning, then served as M1 from then on (see box in **Figure 3B** for the complete list of pairings). Context-dependent preferences were evident in both M1s (see main text for statistics). Other monkeys involved in the study only served as M2.

The conditioning task consisted of randomly interleaved Pavlovian (**Figure 1B**, top) and instrumental conditioning trials (**Figure 1B**, middle). On both trial types, M1 initiated the trial by shifting gaze to a central stimulus ($0.7° \times 0.7°$). After 200 ms of fixation, a cue ($5° \times 5°$) of different shape and/or color appeared in the center and remained on for 1 s on Pavlovian trials and for 300 ms on instrumental trials. Visual cues on Pavlovian trials contained a white outline around the same cues used to convey the same reward outcomes on instrumental trials (**Figure 1C**). On Pavlovian trials, cue onset marked the end of the fixation requirement (i.e., free to look anywhere), and the appropriate reward outcome was delivered. On instrumental trials, however, extinction of the cue was followed by another 200 ms of central fixation before a white target stimulus (1° diameter) appeared at one of eight random locations (eccentricity of 8°). M1 had 1.5 s to shift gaze to the target with in 3.4°. After successful target acquisition, the appropriate reward was delivered. At the onset of reward, M1 was free to look anywhere in the setup before the next trial began for 1 s. Rewards were delivered at approximately the same time for the Pavlovian and instrumental trials after matching the reward timings of the previously occurred instrumental trials (requiring motor responses) to the subsequent Pavlovian trials on a trial-by-trial basis. Data from 120 ± 57 (median $\pm$ SD) and 173 ± 59 correct trials were collected for each pair and the non-social control, respectively.

In the preference task (**Figure 1C**, bottom), M1 again began each trial by shifting gaze to the fixation stimulus. After 200 ms of central fixation, two of the previously learned cues from the

Table 1 | Stimulus–reward pairs used in the experiments.

Stimulus–reward associations				Conditioned pairs on the conditioning trials (M1–M2)	Preference tested pairs on e the preferenctrials (M1–M2)		
R_{SELF}	R_{BOTH}	R_{OTHER}	R_{NONE}				
					MY–MD	MO–MD	MO–MB
				MY–MD	MY–ML	MO–ML	
■	■	■	■	MO–MD	MY–MO	MO–MS	
●	⬟	◆	▲	MO–MY		MO–MY	
▲	●	⬟	◆	MY–C/J		MY–C/J	
■	■		■	MO–C/J		MO–C/J	

*Stimuli used for all individual monkey–monkey (e.g., MY–MD) pairs and monkey–chair/juice (e.g., MY–C/J) controls. On Pavlovian trials, a white outline was present on these cues (e.g., see **Figure 1C**).*

conditioning task appeared as targets at two of eight random locations 8° from the central fixation stimulus, separated by 180° (e.g., **Figures 1A,B**, bottom). Upon target onset, M1 shifted gaze to one or the other target, and the reward outcome associated with that chosen target was delivered. M1 had 1.5 s to shift gaze to the target (±3.4°). Data from 229 ± 88 and 122 ± 78 correct trials were collected for each pair and the non-social control, respectively.

For both tasks, when an error occurred (i.e., failure to maintain fixation after cue onset or inaccurate gaze shift to the peripheral target), the trial was aborted, and a white error square (14.2° × 14.2°) appeared on the screen for 1.5 s. On Pavlovian conditioning trials, errors were defined as failures to maintain fixation after acquiring the fixation point to start a trial. Because these errors were independent of any reward contingencies (i.e., before cue onset), we did not consider them here. On instrumental conditioning and choice trials, errors were defined as either failures to maintain fixation in the beginning of a trial or breaking fixation or not acquiring a target after the reward contingencies were revealed (after cue onset). In practice, almost all errors resulted from monkeys looking up and away from the computer monitor. Error trials were excluded from further analyses.

We calculated a vicarious reinforcement index (VRI) by computing the difference between the frequency of choosing one option (n_A) and the other (n_B) and then normalizing the difference by the sum:

$$\mathrm{VRI} = \frac{n_A - n_B}{n_A + n_B}. \quad (1)$$

In the Self/Both context, n_A and n_B were the number of R_{BOTH} and R_{SELF} choices, respectively, whereas in the Other/None context, they were R_{OTHER} and R_{NONE}, respectively. The VRI always ranged from −1 to 1, with 1 corresponding to M1 always choosing the prosocial option (either R_{BOTH} or R_{OTHER}), −1 corresponding to M1 always choosing the non-prosocial option (either R_{SELF} or R_{NONE}), and 0 corresponding to M1 choosing each of the alternatives equally often.

Saccade reaction times (RTs; time from target onset to movement onset) were computed using a 20°/s velocity crossing threshold on each trial. The frequency of M1 looking at M2 was computed by counting the number of gaze shifts made by M1 into a 25° × 25° window spanning from the center of M2's face during the peri-reward free-viewing period (from the start of reward delivery up to 1 s after reward the completion of the delivery; **Figure 1B**). On non-social control trials, this region was occupied by an operating juice tube and a depository bottle situated in the neckplate of our primate chairs.

RESULTS

MONKEYS EXHIBIT VICARIOUS REINFORCEMENT

Two adult male rhesus monkeys served as actors (M1) and five adult male rhesus monkeys served as recipients (M2; see Materials and Methods). M1 and M2 sat across from each other (**Figure 1A**), and each viewed his own computer screen, which displayed visual cues. On *Pavlovian* trials (**Figure 1B**, top), M1 and M2 both saw the same cue at the center of the display, and juice rewards were delivered to M1 (R_{SELF}), M2 (R_{OTHER}), both M1 and M2 (R_{BOTH}), or neither (R_{NONE}) depending on the color or shape of the cue (**Figure 1C**; **Table 1**). On *instrumental* trials (**Figure 1B**, middle), M1 and M2 again both saw the same cue and a neutral target appeared, to which M1 had to shift gaze for subsequent delivery of juice reward to M1, M2, both M1 and M2, or neither.

Error rates (failure to maintain fixation after cue onset or inaccurate gaze shift to the peripheral target; see Materials and Methods) on the instrumental trials demonstrated that M1 discriminated among the four reward conditions (**Figure 2A**). For both instrumental conditions in which M1 received direct fluid reward, error rates were indistinguishable whether or not M2 was also rewarded (R_{SELF} and R_{BOTH}; $p = 0.54$, Wilcoxon sign rank test; $n = 57$ sessions; **Figure 2A**). In contrast, M1 made significantly more errors on trials with cues that did not result in direct fluid reward to self compared with trials displaying cues that predicted direct fluid reward to self (R_{SELF} or R_{BOTH} versus R_{OTHER} or R_{NONE}; all $p < 0.00001$, Wilcoxon sign rank test; $n = 57$ sessions; **Figure 2A**).

Notably, M1 continued to perform instrumental trials with cues predicting reward to M2 (R_{OTHER}) or no one (R_{NONE}) despite the fact that he was never rewarded in either case and error rates clearly showed that M1 did not prefer these cues [error rates: 71.0 ± 4.3% (mean ± SEM per session) and 84.8 ± 2.8%, respectively]. Critically, M1 made significantly fewer errors when the cue predicted a fluid reward for M2 compared with when

the cue predicted no one would receive a fluid reward, indicating a reinforcing property to observing M2 receive a reward ($p < 0.00001$, Wilcoxon sign rank test; $n = 57$; **Figure 2A**). This pattern of systematically lower error rates on R_{OTHER} compared to R_{NONE} was also evident in each M1 individually (both $p < 0.005$, Wilcoxon sign rank test; $n = 44$ for MY and 13 sessions for MO). In contrast, in a non-social control in which M2 was replaced with a collecting bottle (chair/juice control; see Materials and Methods), the error rates for responding to cues predicting reward to other (R_{OTHER}) and reward to no one (R_{NONE}) were statistically indistinguishable ($p = 0.20$, Wilcoxon sign rank test; $n = 9$ sessions; **Figure 2B**).

The presence of another monkey clearly influenced error rates during conditioning. M1 made fewer errors overall in the non-social control compared to the social trials (total error rates: 15.5 ± 3.8% versus 47.6 ± 2.5%, $p < 0.00001$, Wilcoxon rank sum test; $n = 57$; **Figure 2A**). The higher error rates on the social compared to the non-social control trials could be attributed to increased attentional demands due to the presence of another monkey (e.g., bystander effect). Error rates during the conditioning trials demonstrate that rhesus monkeys value rewards to self more than they value rewards to others, as expected. Nonetheless, the fact that M1 continued to participate when only M2 was rewarded directly with juice suggests that observing another monkey receive a reward is vicariously reinforcing.

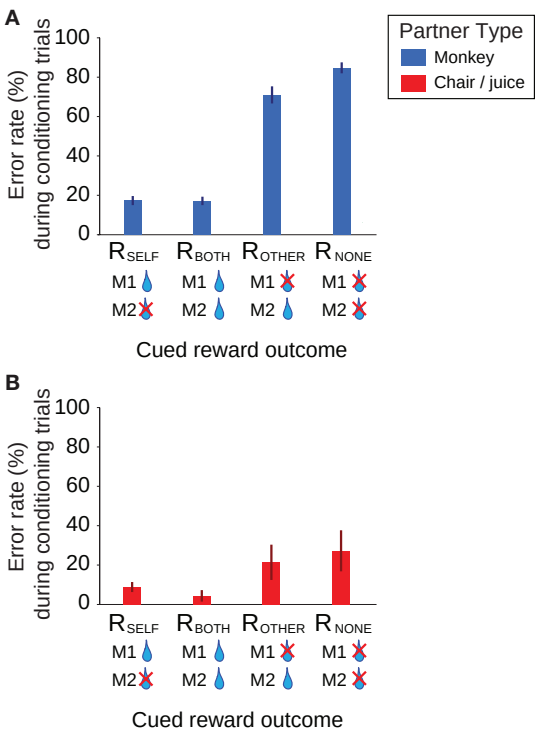

FIGURE 2 | Error patterns during instrumental conditioning demonstrate rhesus macaques are sensitive to other's rewards. (A) Error rates (excluding first sessions) on the instrumental conditioning trials (mean of sessions ± SEM) in M1–M2 conditions ($n = 57$ sessions). **(B)** Error rates in the non-social (M1–C/J) controls ($n = 9$ sessions). Same format as in **(A)**.

CONTEXT-DEPENDENT MANIFESTATION OF VICARIOUS REINFORCEMENT

Subsequently, we used a two alternative forced task (preference task; **Figure 1B** bottom) to directly test the hypothesis that observing another monkey receiving a reward is vicariously reinforcing. In the preference task, M1 chose between pairs of previously conditioned cues (R_{SELF} versus R_{BOTH}, or R_{OTHER} versus R_{NONE}) by shifting gaze to one of them. Critically, rewards were matched between the available choices in each condition – that is, M1 chose between R_{OTHER} and R_{NONE} [Other/None condition (purely vicarious context); M1 never directly rewarded with juice] or between R_{BOTH} and R_{SELF} (Self/Both condition; M1 always rewarded with juice). We hypothesized that cues would acquire value vicariously via Pavlovian and instrumental conditioning, and that differential cue values would be expressed as systematic preferences in this choice task.

As expected, error rates in the preference task were consistent with a preference for receiving direct fluid reward in the Self/Both condition (error rate: 0.8 ± 0.2%; $n = 64$ sessions), compared to no fluid reward in the Other/None condition, in which M1 was never rewarded (12.6 ± 1.8%; $p < 0.00001$, Wilcoxon sign rank test; $n = 64$). Remarkably, however, M1 performed about 88% of trials in which he was not directly rewarded with fluid. Again, as in the conditioning trials, M1 made significantly fewer errors during the non-social control ($n = 13$ sessions) compared to when M2 was present ($p < 0.001$, Wilcoxon rank sum test). M1 was significantly more willing to complete trials which resulted in no reward to M1 during the preference trials compared to the Pavlovian conditioning trials (correct rate: 87.4 ± 1.8% versus 22.1 ± 2.7%, $p < 0.00001$, Wilcoxon rank sum test). This is consistent with prior observations in rhesus macaques that voluntary choices are more motivating than simple operant responses in the conditioning tasks (Suzuki, 1999).

The critical question was whether M1 acquired an intrinsically rewarding preference, through vicarious reinforcement, for rewarding M2 in the absence of rewarding self (R_{OTHER}). The choice preferences of M1 demonstrated that cues indeed acquired strong motivational associations even when M1 received no direct reward. M1 consistently preferred R_{OTHER} (82.5 ± 1.1%) over R_{NONE} (17.5%; $p < 0.00001$, Wilcoxon signed rank test; $n = 64$ sessions), even though M1 was never directly rewarded with juice in this context (**Figure 3A**). Critically, this preference was absent in the non-social control when M2 was removed from the experimental room and replaced by an operating juice tube and a collection bottle [**Figure 3A**; 54.7 ± 3.8 (R_{OTHER}) versus 45.3% (R_{NONE}), $p = 0.17$, Wilcoxon sign rank test; $n = 13$]. In contrast, in the Self/Both context, M1 consistently preferred R_{SELF} (80.3 ± 1.0%) over R_{BOTH} (19.7%; $p < 0.00001$, Wilcoxon sign rank test; $n = 64$), even though either choice led to the same physical juice reward for M1 simultaneously (**Figure 3A**). This pattern was again absent in the non-social control [**Figure 3A**; 48.3 ± 1.3 (R_{SELF}) versus 51.7% (R_{BOTH}), $p = 0.06$, Wilcoxon sign rank test; $n = 13$]. We observed the context-dependent patterns of behavior in each M1 separately [percentage of choosing R_{OTHER} (MY and MO): 86.7 ± 1.5 and 80.7 ± 1.4%; percentage of choosing R_{SELF}: 85.4 ± 1.6 and 79.6 ± 1.1%].

We further quantified M1's preferences by calculating a VRI, a contrast ratio varying from −1 to 1, with positive values indicating preferences for R_{OTHER} over R_{NONE} (Other/None condition)

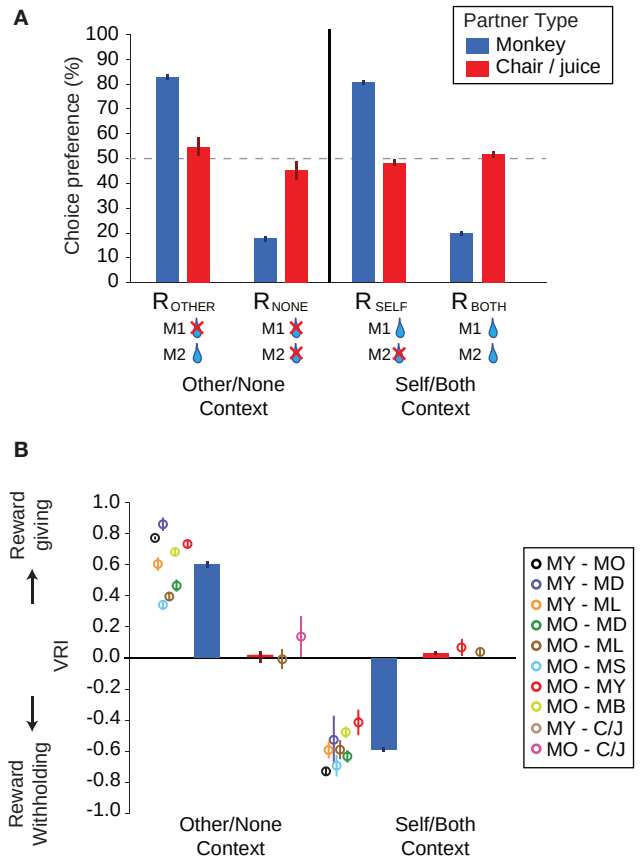

FIGURE 3 | Context-dependent vicarious reinforcement drives the expression of other-regarding preferences in rhesus macaques. (A) Choice preferences (median of all sessions ± SEM) in the Other/None and Self/Both contexts across M1–M2 pairs (8 pairs, 64 session) and M1–chair/juice controls (2 pairs, 13 sessions). **(B)** Choice preferences expressed as VR indices (median of all sessions ± SEM) in the Other/None and Self/Both contexts across M1–M2 pairs (see box for individual pair medians and standard deviations (SDs) for their ranges) and M1–chair/juice controls. Bars are color-coded by the partner type in both panels (see box in **A**).

or R_{BOTH} over R_{SELF} (Self/Both condition) and 0 indicating indifference (see Materials and Methods). Analysis of the index led to similar results. In the Other/None condition, M1 preferred to reward M2 (VRI: 0.60 ± 0.02, significantly different from 0, $p < 0.00001$, Wilcoxon sign rank test; $n = 64$ sessions; **Figure 3B**), and this pattern was absent in the non-social control (0.11 ± 0.08, $p = 0.18$, Wilcoxon sign rank test; $n = 13$; **Figure 3B**). In the Self/Both context, however, M1 preferred to withhold reward from M2 (−0.58 ± 0.02, $p < 0.00001$, Wilcoxon sign rank test; **Figure 3B**), and this pattern was only weakly evident in the non-social control (0.06 ± 0.03, $p = 0.06$, Wilcoxon sign rank test; **Figure 3B**). Again, we observed the same pattern in each M1 separately [Other/None context (MY and MO): 0.70 ± 0.03 and 0.56 ± 0.03; Self/Both context: −0.65 ± 0.03 and −0.55 ± 0.02; all $p < 0.00001$, Wilcoxon sign rank test; $n = 19$ and 45, respectively]. These preferences remained stable over the course of data collection (**Figure 4**). Crucially, the VRI indices in the Other/None and Self/Both contexts never crossed over.

SOCIAL VARIABLES INFLUENCE VICARIOUS REINFORCEMENT

The magnitudes of the VRI were idiosyncratic to individual pairs of monkeys. Such differences were apparent from the very beginning of testing and remained more or less stable (**Figure 4**). We tested whether a specific social variable could explain this individual variability. First, we examined social status, which is known to influence social behaviors in both young children and non-human animals (Hawley, 1999), and observational learning has been implicated in how monkeys acquire social hierarchical information (Cheney and Seyfarth, 1990). We found that M1 was more willing to share reward if M1 was dominant to M2 in the Self/Both context ($n = 4$ out of 8). Specifically, M1 was more likely to choose R_{BOTH} in the Self/Both context [VRI: −0.54 ± 0.03 (M1 is dominant) versus −0.65 ± 0.03 (M1 is subordinate), $p < 0.01$, Wilcoxon rank sum test], but not necessarily R_{OTHER} in the Other/None context (0.62 ± 0.02 versus 0.58 ± 0.04, $p = 0.57$, Wilcoxon rank sum test), if M1 is dominant to M2.

Second, we examined whether the familiarity of individuals in each pair biased choices by analyzing the housing locations of M1 relative to M2 in the colony room, which served as our measure of familiarity. It has been documented that social interaction behaviors increase with familiarity in both humans and monkeys (Preston and de Waal, 2002). We therefore reasoned that monkeys who could directly view each other (housed on opposite sides, compared to on same sides) would be more familiar and thus more likely to reward others. We found that VRI in the Other/None context was higher if M1 and M2 were housed on opposite sides ($n = 4$ out of 7) of the colony room, with direct visual access to each other. That is, M1 was more likely to choose R_{OTHER} in the Other/None context [0.71 ± 0.02 (opposite side) versus 0.53 ± 0.03 (same side), $p < 0.0001$, Wilcoxon rank sum test], but not necessarily R_{BOTH} in the Self/Both context (−0.60 ± 0.03 versus −0.57 ± 0.02, $p = 0.19$, Wilcoxon rank sum test), if he could see him while in his home cage. Together, these findings suggest that individual variability in vicarious reinforcement (**Figures 3B and 4**) is at least partially influenced by both social dominance and social familiarity, although our limited sample size and types preclude strong conclusions.

MONKEYS OBSERVE THE REWARDING EVENTS OF OTHERS

After monkeys expressed their choice, they were permitted to freely look about (**Figure 1B**). During this free-viewing period, M1 often shifted gaze toward the face of M2, and the overall rate of shifting gaze depended on the reward outcome for M1 [**Figure 5A**; 20.5 ± 3.6% (median ± SEM of the average between R_{OTHER} and R_{NONE}) versus 3.0 ± 2.5% (R_{SELF} and R_{BOTH}), $p < 0.00001$, Wilcoxon sign rank test; $n = 64$ sessions]. Critically, however, M1 looked at M2 more frequently after choosing to reward him over no one in the Other/None condition (R_{OTHER}, 25.4 ± 4.1%; R_{NONE}, 16.7 ± 5.8%, $p < 0.0005$, Wilcoxon sign rank test). We found a significant effect (frequency of gaze after choosing $R_{OTHER} > R_{NONE}$) in both M1s separately [MY: 23.1 ± 1.6 versus 15.4 ± 2.3% ($p < 0.005$; $n = 19$); MO: 26.1 ± 5.6 versus 17.9 ± 8.1% ($p < 0.01$; $n = 45$), Wilcoxon sign rank test]. Thus, our observation confirms that there is a link between social attention and vicarious reinforcement.

By contrast, in the non-social control ($n = 13$ sessions), looking behavior was greatly reduced across all reward outcomes, compared to the social conditions (R_{SELP}, R_{OTHER}: $p < 0.01$; R_{BOTH}: $p = 0.12$; R_{NONE}:

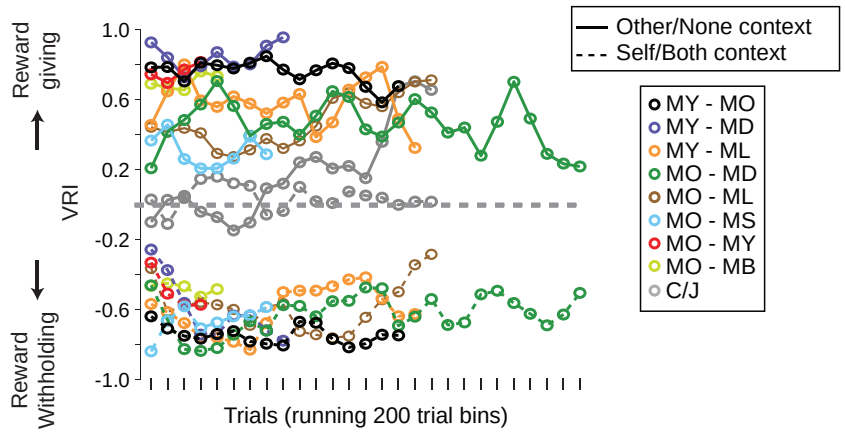

FIGURE 4 | Temporal progression (moving 200-trial bins with a step size of 100 trials) of context-dependent VR indices for individual M1–M2 pairs (8 pairs, 64 sessions) and M1–C/J pairs (2 pairs, 13 sessions; see box for pair identities). Data points on the right show individual pair medians and SDs across all trial bins for each pair.

$p = 0.01$, Wilcoxon rank sum test; **Figure 5A**). Critically, M1 neither looked at the juice bottle more often after choosing R_{OTHER} over R_{NONE} in the Other/None condition ($p = 0.34$, Wilcoxon sign rank test), nor after choosing R_{BOTH} over R_{SELF} in the Self/Both condition ($p = 0.94$, Wilcoxon sign rank test). The only factor that explained looking behavior in the non-social control was whether or not M1 was directly rewarded with juice (R_{SELF} and R_{BOTH} versus R_{OTHER} and R_{NONE}, $p < 0.0005$, Wilcoxon rank sum test). Thus, reward consumption by another monkey strongly recruits attention in the absence of direct reward to self, suggesting vicarious reinforcement may be mediated by social attention circuits in the brain (Klein et al., 2009).

SACCADE REACTION TIMES REVEAL THE INTERNAL DELIBERATIVE PROCESS

The pattern of saccade RTs on choice trials further corroborates the hypothesis that rewarding self was more valued than any other alternatives (**Figure 5B**; RTs for $R_{SELF} < R_{BOTH} < R_{OTHER} < R_{NONE}$; all comparisons $p < 0.00001$, Wilcoxon sign rank; $n = 64$ sessions). Generally, M1 responded more quickly whenever he chose to directly reward himself with juice. Nonetheless, M1 responded faster when he chose to reward M2 than when he chose to reward no one at all. These results were obtained for each M1 separately (all comparisons $p < 0.01$ for each M1, Wilcoxon sign rank test; $n = 19$ and 45 sessions for MY and MO, respectively). Importantly, in the absence of M2 (non-social control; $n = 13$ sessions), RTs across different reward outcomes remained more or less flat (**Figure 5A**). RTs were indeed slower overall in the presence of M2, perhaps due to an additional attentional load induced by the presence of M2 (blue versus red traces in **Figure 5B**; all comparisons $p < 0.005$, except $p = 0.46$ for R_{SELF} conditions, Wilcoxon rank sum test).

Given that monkeys generally respond more slowly when they anticipate smaller rewards (Kawagoe et al., 1998; Roesch and Olson, 2004), we inferred the subjective reward value of the four conditions to be $R_{SELF} > R_{BOTH}$ and $R_{OTHER} > R_{NONE}$. These inferred subjective reward values, which were absent in the non-social control (**Figure 5B**), predict the relative preferences between cues observed in the preference task (**Figure 3**). Specifically, M1 chose R_{SELF} over R_{BOTH} in the Self/Both condition and showed faster RT for choosing R_{SELF}, whereas M1 chose R_{OTHER} over R_{NONE} in the Other/None condition and showed faster RT for choosing R_{OTHER}.

DISCUSSION

We demonstrated that social preferences of rhesus macaques – nonhuman primates that live in large, hierarchical, mixed-sex social groups and who last shared a common ancestor with humans some 25 million years ago – could be shaped by vicarious reinforcement in a context-specific manner. Monkeys systematically preferred to provide juice reward to others rather than to no one, as if observing others drink is vicariously rewarding. In contrast, monkeys systematically withheld reward from others when confronted with the options to either consume reward alone or share reward. Increased social attention to M2 (i.e., the increased rate of gaze shift to M2) in the Other/None context corroborates enhanced vicarious reinforcement during social decision-making.

Rewarding the other monkey without any opportunity to reward self is a uniquely vicarious form of reward. Such vicarious reinforcement may be driven by an intrinsic tendency to observe the experience of others to gather information, as can occur in foraging (Cheney and Seyfarth, 1990; Valone and Templeton, 2002). It is possible, however, that monkeys simply find feedback to their actions intrinsically rewarding. For instance, choosing to reward others in the Other/None context is the only option that results in a salient feedback that could serve as a secondary reinforcer or confirmation that a chosen action has resulted in a noticeable change in the environment. However, the preference to reward only self in the Self/Both context makes this possibility less likely (although the actor monkeys may have been less interested in the other monkeys due to receiving reward or the competitiveness evoked by this context), since choosing to reward both would also result in salient feedback. Furthermore, the absence of preference in the non-social control trials indicates that mere actions that result in fluid delivery are not sufficient to drive vicarious reinforcement, suggesting that the presence of a social agent is required. Notably, however, monkeys still showed high error rates (71%) in the conditioning trials when

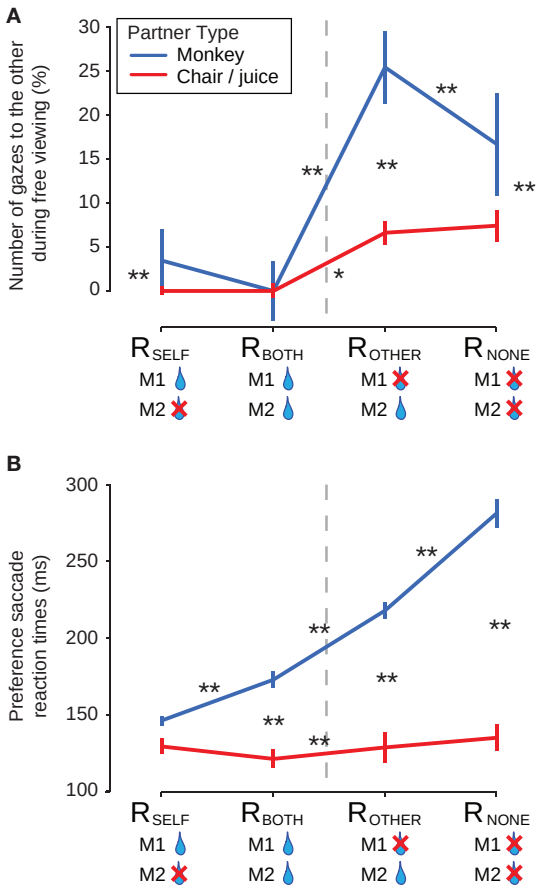

FIGURE 5 | Gaze behavior reflects the internal social deliberation process. (A) The frequency of gaze shifts (%; median ± SEM of individual sessions; 64 M1–M2 sessions, and 13 M1–C/J sessions) toward the face region of M2 (or toward the juice tube and the bottle on control trials) during the free-viewing period (after choosing a reward option) of the preference task. **(B)** Saccade reaction times (RTs; median ± SEM of individual sessions; 64 M1–M2 pairs, and 13 M1–C/J pairs) for choosing different reward outcomes in the choice task. Asterisks indicate significance in **(A,B)**: $*p < 0.05$; $**p < 0.005$ by Wilcoxon sign rank test across same partner types, and Wilcoxon rank sum test across different partner types. Dashed vertical lines distinguish Self/Both and Other/None contexts.

the visual cues predicted reward to other monkey only. Interestingly, the error rates were much lower (<13%) when monkeys confronted a choice between Other/None in the preference task. This is consistent with observations that rhesus macaques are much more motivated when making voluntary choices compared to making simple operant responses (Suzuki, 1999). Still, the atypically large error rates observed in the conditioning trials seems to be consistent with the competitiveness of rhesus macaques, and may highlight differences between humans and rhesus macaques (also see below).

In contrast, any of the two available options from the Self/Both context results in direct fluid reward. The preference to withhold reward from others in this particular context may reflect a potential diminishment of reward during simultaneous consumption, possibly due to the uncertainty of the quantity or quality of reward delivered to others. Reward withholding behavior may also arise from rhesus monkeys' natural competitive tendencies (Anderson and Mason, 1978). For instance, from an ecological standpoint, sharing food with other individuals always reduces the amount of potential food available to oneself. Moreover, reduced rates of attending to M2 in the Self/Both context may further mitigate vicarious reinforcement during social decision-making. We observed a small but significant tendency to withhold less if actor monkeys were dominant to recipient monkeys, although our limited sample size and types preclude strong conclusions. This is consistent with a recent study in long-tailed macaques (*M. fascicularis*) showing that dominant macaques are more "prosocial" toward subordinates (Massen et al., 2010). Dominant monkeys might be more likely to engage in such positive other-regarding behaviors to sustain their rank and promote group cohesion, especially when there is no added cost, as in the Self/Both context. By extension, we would predict humans to choose to reward both individuals in an analogous monetary version of the Self/Both context, as long as the monetary reward was the same for both individuals and the amount of reward was undiminished by sharing (i.e., non-competitive situation). If the monkeys were clearly aware that they both always received the same amount of juice with an infinite amount of resources, they might also increase preferences to reward both monkeys. Alternatively, it is also plausible that the rhesus macaques, unlike humans, have a difficult time in ignoring their naturally competitive cognitive set.

It is critical to emphasize the dramatic differences in preferences between Self/Both and Other/None contexts. If the actor monkeys always found it valuable to reward the recipient monkey, then we would have expected the monkeys to prefer to reward both in the Self/Both context. Alternatively, if the monkeys always found rewards delivered to the other monkey to be aversive, perhaps due to perceived competition, then we would have expected the monkeys to prefer to reward none in the Other/None context. Instead, we observed a clean dissociation of preferences depending on social context, suggesting that different reward contingencies strongly influenced decisions. This is consistent with our findings that RTs, frequency of attention directed to the other monkey, and error rates were clearly different between choosing to reward both and choosing to only reward other. (Please also see our response above for situation-specific social behaviors in humans and monkeys.) The behavioral and neural mechanisms responsible for such context-dependent social decision-making would provide new insights into the social flexibility characterizing the behavior of macaques and other primates, including humans.

We hypothesize that vicarious experiences are processed as rewarding signals in the brain, and are mediated by neurons in homologous circuits governing social perception and reward learning in non-human primates and humans (Bandura and Rosenthal, 1966; Fehr and Camerer, 2007; Lohrenz et al., 2007; Lee, 2008; Hayden et al., 2009; Mobbs et al., 2009). One plausible mechanism is that the overlapping populations of neurons respond both to rewards to self and rewards to another individual. Such vicarious reward could motivate social interactions as well as underlie observational learning and mutualistic behaviors such as alliance formation, social grooming, and group cohesion (Fehr and Fischbacher, 2003; Takahashi et al., 2009). Modulation of vicarious

reward signals by social variables such as dominance or familiarity could further provide a mechanism promoting socially adaptive behavior toward specific individuals.

Observing rewarding events of others has been shown to systematically and effectively modulate neural activity in classic reward areas in humans, including ventral striatum, ventromedial prefrontal cortex, and anterior cingulate cortex (Mobbs et al., 2009; Lombardo et al., 2010). Moreover, the anterior cingulate cortex has been implicated in evaluating social information with respect to others (Takahashi et al., 2009). Dorsolateral and ventromedial prefrontal cortices in humans have been implicated in observing an action and observing reward outcome of others, respectively (Burke et al., 2010). Observational fear conditioning in mice depends on affective pain circuitry including anterior cingulated cortex (Jeon et al., 2010). Activation of these neural circuits by vicarious outcomes may be the neural substrate that ultimately promotes empathy and altruism, as well as observational learning.

These findings suggest that vicarious reinforcement is rooted in fundamental cognitive mechanisms that evolved early in the primate clade. Throughout primate evolution, vicarious reinforcement may have served as a core building block for complex social behaviors such as cooperation and competition, while facilitating observational learning and group coordination. We also note that our experimental design provides a powerful tool for exploring the neural mechanisms underlying social learning and decision-making and thus will be of use to comparative psychologists and neuroscientists alike.

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Neuronal reference frames for social decisions in primate frontal cortex

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Social decisions are crucial for the success of individuals and the groups that they comprise. Group members respond vicariously to benefits obtained by others, and impairments in this capacity contribute to neuropsychiatric disorders such as autism and sociopathy. We examined the manner in which neurons in three frontal cortical areas encoded the outcomes of social decisions as monkeys performed a reward-allocation task. Neurons in the orbitofrontal cortex (OFC) predominantly encoded rewards that were delivered to oneself. Neurons in the anterior cingulate gyrus (ACCg) encoded reward allocations to the other monkey, to oneself or to both. Neurons in the anterior cingulate sulcus (ACCs) signaled reward allocations to the other monkey or to no one. In this network of received (OFC) and foregone (ACCs) reward signaling, ACCg emerged as an important nexus for the computation of shared experience and social reward. Individual and species-specific variations in social decision-making might result from the relative activation and influence of these areas.

Social cohesion depends on vicarious identification with members of one's group. In social situations, we are aware of our actions and their consequences, but also consider those of others, especially those with whom we might interact[1]. We also estimate the internal states of others, perhaps by simulation[2], which in turn shapes our future actions. Social situations can drive observational learning[3], and other-regarding preferences influence neural computations that ultimately result in cooperation, altruism or spite[4,5]. Disruptions of neural circuits involved in other-regarding processes may underlie social deficits attending neuropsychiatric conditions like autism[6]. Human imaging and clinical studies have found critical links between social deficits and abnormal brain activity in frontal cortex and its subcortical targets[7].

Neural circuits involved in reinforcement learning and decision-making are crucial for normal social interactions[8]. Critical nodes include ACC[9–11], the OFC[12–17] and subcortical areas, such as the dopaminergic ventral tegmental area, substantia nigra[18,19], the striatum[20,21], the lateral habenula[22] and the amygdala[23]. Neuroimaging studies in humans report activation of some of these areas by both giving rewards and receiving rewards[24–28], and lesions to some of these areas result in impaired social decision-making[7]. These findings suggest that a generic circuit for reward-guided learning and decision-making mediates social decisions[8]. Despite this evidence, and the clear clinical relevance of understanding the neurobiology of social decision-making, precisely how neurons in any of these areas compute social decisions remains unknown, largely because of difficulties in implementing social interactions while simultaneously studying neuronal activity and controlling contextual variables. Single-unit recording studies in nonhuman animals, such as macaques, making social decisions of similar complexity to those made by humans would help to address this gap.

We implemented a reward-allocation task in pairs of rhesus macaques while recording from single neurons in three critical nodes in the decision-making network, namely the ACCg, ACCs and OFC. Our study capitalized on monkeys' willingness to engage with a social partner via an interposed computer system while simultaneously controlling the sensory and reward environment. We specifically matched choices for the reward outcomes directly received by the actor monkey (decision maker) and controlled for potential secondary acoustic reinforcement effects associated with delivering juice to the recipient monkey. In these conditions, we found regional biases in the encoding of social decision outcomes with respect to self and another individual. In this network of received (OFC) and foregone (ACCs) reward signals, ACCg emerged as an important nexus for the computation of shared experience and social reward.

RESULTS

Summary of behavior in the reward-allocation task

On half of the trials, termed choice trials, actor monkeys chose between visual stimuli that led to juice being delivered either to themselves (self reward), to the recipient monkey (other reward) or to neither monkey (neither reward). Offers appeared in pairs of three types, which defined self:neither trials, self:other trials and other:neither trials (**Fig. 1**). On the other half, termed cued trials, monkeys observed a single cue that indicated that self, other or neither rewards would be delivered by the computer.

Actor monkeys performed the reward-allocation task well (**Fig. 2a**), as indicated by the low mean number of incomplete trials per session (4.6 ± 0.2% (s.e.m.); Online Methods), even when the actors had no chance of obtaining juice rewards themselves, which was the case for other:neither choice trials and for other and neither cued trials (7.4 ± 0.3%).

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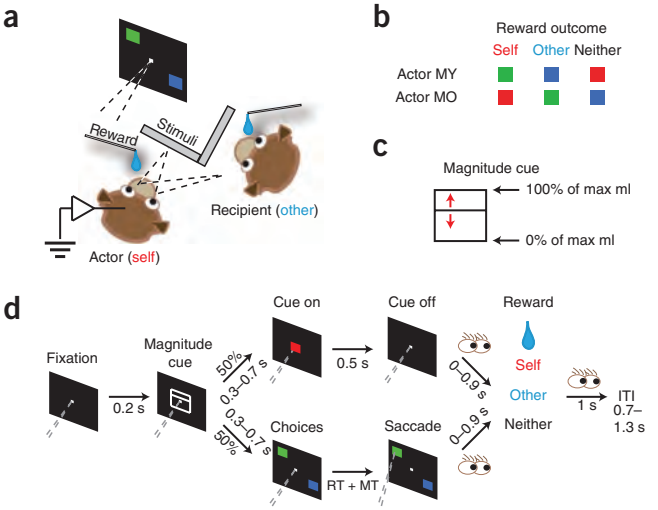

Figure 1 Reward-allocation task. (**a**) Experimental setup for an actor and a recipient monkey. (**b**) Stimulus-reward outcome mappings for reward delivered to actor (self), recipient (other) or no one (neither), shown separately for each actor. (**c**) Magnitude cue used to indicate juice amount at stake for each trial (see **d**). The position of the horizontal bisecting line specified the percentage of maximum reward that was possible. (**d**) Task structure (see Online Methods). Top fork, cued trials; bottom fork, choice trials. Dashed gray lines show the angle of the actor's gaze, converging on the fixation point. Eye cartoons indicate times at which the actor could look around. ITI, inter-trial interval; MT, movement time; RT, reaction time.

Actor monkeys also made significantly fewer errors when they made active decisions (choice trials) than when there was no choice (cued trials) or when there was no reward at stake for themselves ($P < 0.0001$, Welch two-sample t test). These findings suggest that monkeys find it rewarding to actively choose what to do and can be motivated to work without direct reinforcement.

Reaction times often serve as a proxy for motivation in incentivized tasks[29–33]. Reaction times for making different choices demonstrate that actors discriminated the reward types and had orderly preferences amongst them[29,33]. Actors were fastest to choose self rewards, followed by other rewards and neither rewards (**Fig. 2b**). Self versus other reaction times differed by a mean of 39 ms ($P < 0.0001$, Welch two-sample t test); other versus neither reaction times differed by a mean of 20 ms ($P < 0.0001$). The ordered reaction times by monkeys making choices in the reward allocation task suggest that rewarding self is more reinforcing than rewarding the recipient, which is in turn more reinforcing than rewarding no one[33].

Finally, actor monkeys shifted gaze to the recipients more frequently following juice delivery to them than after juice delivery to themselves or to neither monkey, consistent with greater interest in the actions of the other monkey when he was rewarded (**Supplementary Fig. 1**). Taken together, these observations support the conclusion that the actor monkeys were acutely aware of the difference between self, other and neither reward outcomes[33].

We quantified decision preferences by calculating a contrast ratio based on actors' choices (equation (1), Online Methods). Consistent with our previous reports[33,34], actors preferred self rewards over other or neither rewards, but preferred other over neither rewards (**Fig. 2c**). On self:neither and self:other trials, actor monkeys almost always chose to reward self (preference index, mean ± s.e.m.: self:neither, −0.99 ± 0.00; self:other, −0.99 ± 0.00; significantly different from zero: both $P < 0.0001$, one sample t test; **Fig. 2c**). In contrast, on other:neither trials, actors preferred to allocate rewards to the recipient monkey (0.17 ± 0.01, $P < 0.0001$, one sample t test; **Fig. 2c**). We observed similar choice preferences for each actor individually (**Supplementary Fig. 2**).

We previously found that the preference to allocate reward to the other monkey is enhanced by greater familiarity between the two animals and is abolished if the recipient is replaced with a juice collection bottle[33]. We also observed that reward withholding is reduced when actor monkeys are dominant toward recipients, and that the variability and the degree of preferences often depend on the identity of the recipients[33]. Furthermore, we found that actor monkeys prefer to deliver juice to themselves than to both themselves and the recipient simultaneously, perhaps reflecting the competitive nature of simultaneously drinking juice, a resource controlled outside of experimental sessions to motivate performance and often monopolized by

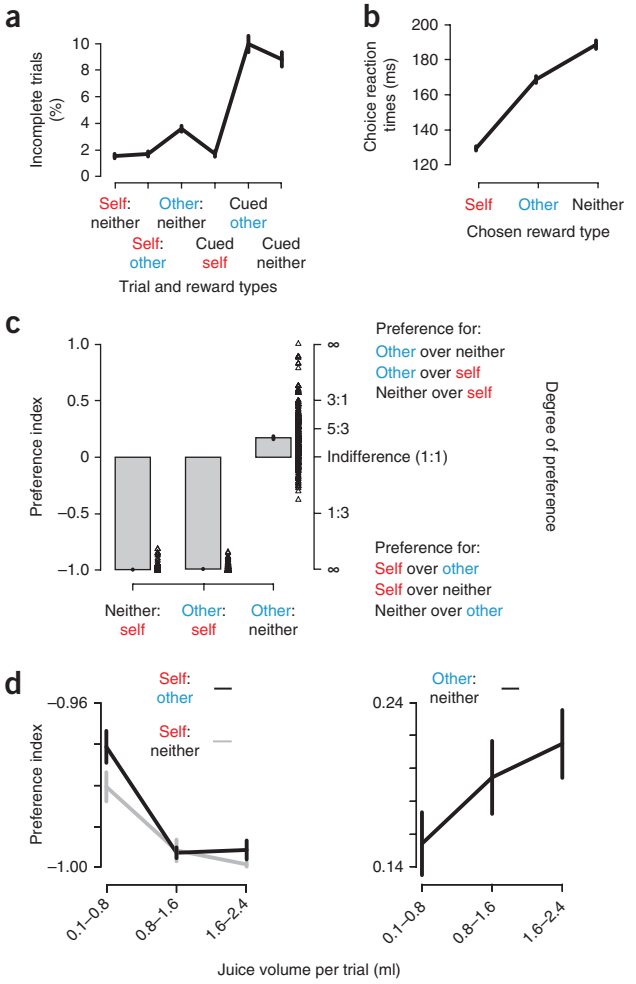

Figure 2 Behavior in the reward-allocation task. (**a**) Proportions of incomplete trials (mean ± s.e.m.) (see Online Methods) during the reward-allocation task. (**b**) Choice reaction times (ms) from trials in which rewards were chosen for self, other or neither (mean of session medians ± s.e.m.). (**c**) Choice preferences (preference index, mean ± s.e.m.) as a function of reward outcome contrasts. Data points next to each bar show the biases for individual sessions. The degree of preference axis on the right shows the range of preference indices in ratio terms. (**d**) Choice preferences (mean ± s.e.m.) as a function of reward magnitude on 219 single-unit sessions collected with the magnitude cue.

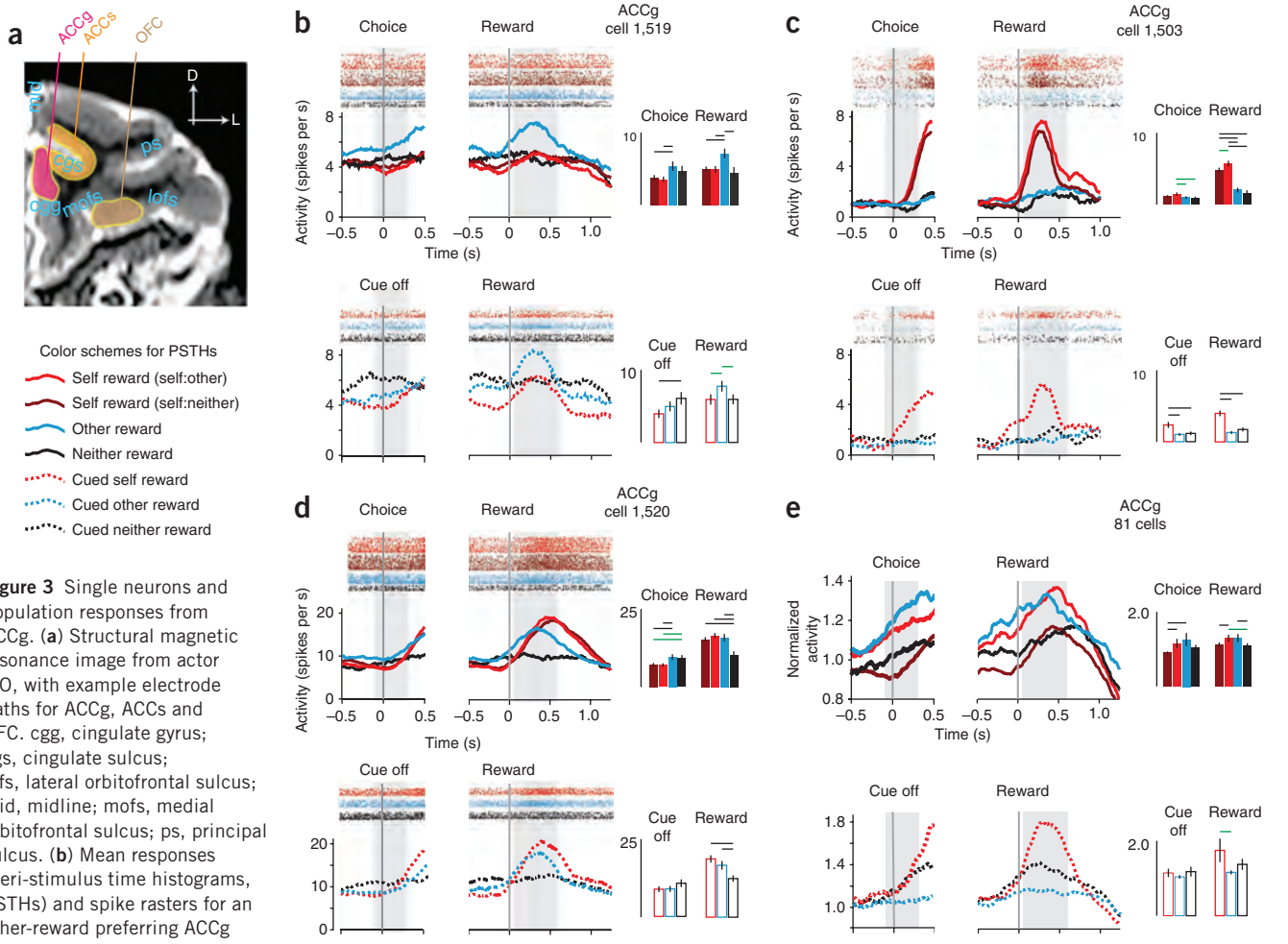

Figure 3 Single neurons and population responses from ACCg. (**a**) Structural magnetic resonance image from actor MO, with example electrode paths for ACCg, ACCs and OFC. cgg, cingulate gyrus; cgs, cingulate sulcus; lofs, lateral orbitofrontal sulcus; mid, midline; mofs, medial orbitofrontal sulcus; ps, principal sulcus. (**b**) Mean responses (peri-stimulus time histograms, PSTHs) and spike rasters for an other-reward preferring ACCg neuron on choice trials (upper, solid traces) and cued trials (lower, dashed traces). Data are aligned to choice/cue offset (left) and reward onset (right) for each reward outcome. Bar histograms on right show mean ± s.e.m. activity from the two epochs (gray regions). Color codes for PSTH traces and histograms are shown below. (**c**) PSTHs and spike rasters for a self-reward preferring ACCg neuron. (**d**) PSTHs and spike rasters for a shared self and other reward–preferring ACCg neuron. (**e**) Normalized choice/cue epoch and reward epoch responses for 81 ACCg neurons. Data in **c**–**e** are presented as in **b**. In all bar histogram insets, the horizontal lines above different conditions indicate significance differences (black, $P < 0.05$ by paired t test; green, $P < 0.05$ by bootstrap test).

dominant monkeys living in pairs with subordinate monkeys in their home cages[33] (M.L.P., unpublished observation). Finally, exogenously increasing oxytocin levels in the CNS amplifies actors' preference to allocate reward to the other monkey over no one[34]. Taken together, these patterns of behavior endorse the fundamentally social nature of the reward-allocation task.

We also found that preferences scaled with the magnitude of juice on offer. With larger amounts of juice at stake, actors became more motivated to receive rewards (self:neither and self:other, slope significantly different from zero: both $P < 0.001$, type II regression) and to allocate rewards to the other monkey over no one (other:neither, $P < 0.05$) (**Fig. 2d**). These findings suggest that both direct and vicarious reinforcement processes that motivate social decisions are magnified by reward magnitude[25–27].

Differential encoding of social decision outcomes

We recorded the activity of single neurons in ACCg ($n = 81$), ACCs ($n = 101$) and OFC ($n = 85$) from two actor monkeys (**Fig. 3a**) during the reward-allocation task, and analyzed the data for both a choice/cue epoch and a reward epoch (Online Methods; data for individual monkeys are shown in **Supplementary Fig. 3**). Overall, we found notable similarities in activity and functional classes across the choice and reward epochs (**Supplementary Fig. 4**). We examined single-neuron and population responses from ACCg (**Fig. 3**), ACCs and OFC (**Fig. 4**), followed by further quantifications in each region (**Fig. 5**).

ACCg contained neurons selective for allocating rewards to another individual, receiving rewards or both. One class of ACCg neuron (**Fig. 3b**) preferentially responded when actors chose to allocate reward to recipients. On choice trials, this example neuron discharged more strongly when the actor chose other rewards (7.12 ± 0.66 (mean and s.e.m.), spikes per s) compared with self rewards on either self:neither or self:other trials (4.95 ± 0.36 and 4.93 ± 0.45 spikes per s, respectively; both $P < 0.01$, Welch two sample t test), and also preferred other rewards over neither rewards (4.44 ± 0.79 spikes per s, $P < 0.05$). This neuron did not differentiate self from neither rewards ($P = 0.97$, Welch two sample t test). On cued trials, this neuron only weakly preferred other over self or neither rewards (both $P = 0.08$, Welch two sample t test; **Fig. 3b**).

In contrast, another class of ACCg neuron (example neuron in **Fig. 3c**) responded selectively for choosing self rewards. The example neuron discharged more when the actor chose to reward himself on self:neither and self:other trials (4.77 ± 0.38 and

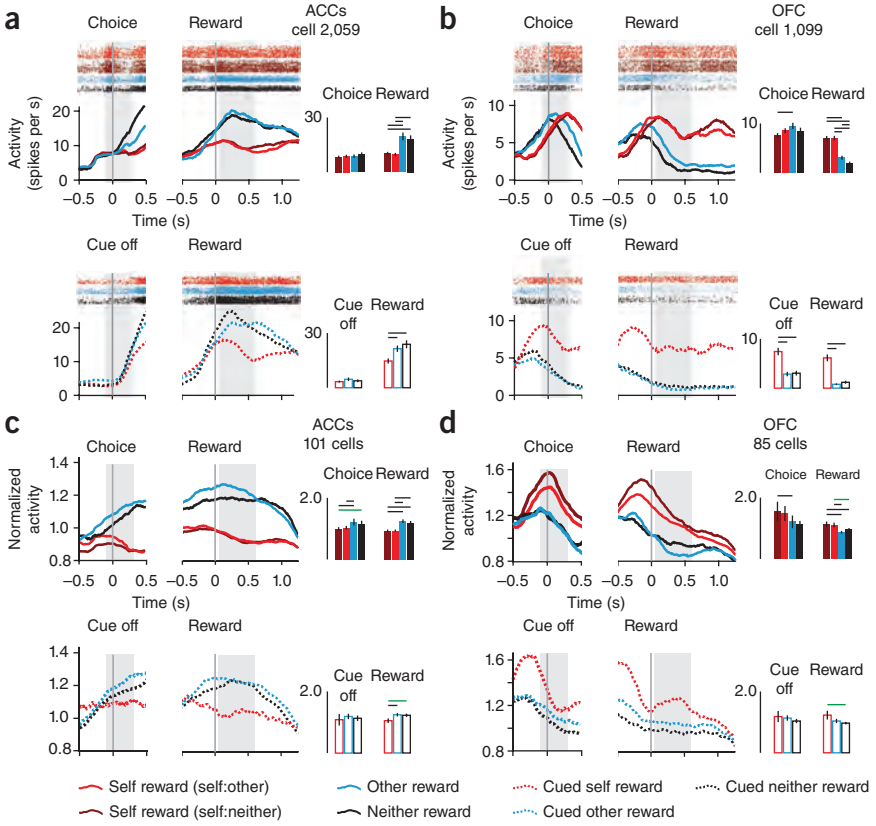

Figure 4 Single neurons and population responses from ACCs and OFC. (**a**) PSTHs and spike rasters for a single ACCs neuron preferring forgone rewards. Data are aligned to choice/cue offset (left) and reward onset (right) for each reward outcome. Bar histograms on right show mean ± s.e.m. activity from the two epochs (gray regions). (**b**) PSTHs and spike rasters for a single OFC neuron preferring self reward. (**c**) Normalized reward epoch responses of 101 ACCs neurons. (**d**) Normalized choice/cue epoch and reward epoch responses of 85 OFC neurons. In all panels, data are presented as in **Figure 3**.

5.70 ± 0.41 spikes per s, respectively) compared with choosing other and neither rewards (2.02 ± 0.32 and 1.60 ± 0.39 spikes per s, respectively) (all $P < 0.0001$, Welch two sample t test; **Fig. 3c**). Moreover, it showed stronger responses when the actor monkey received rewards in self:other than in self:neither context, but this effect did not reach statistical significance ($P = 0.10$, Welch two sample t test). On cued trials, this neuron preferred self over other or neither rewards (both $P < 0.0001$, Welch two sample t test). For both choice and cued trials, the response did not differentiate other and neither rewards (both $P > 0.23$, Welch two sample t test).

Finally, a third class of ACCg neuron (example neuron in **Fig. 3d**) responded equivalently to both received rewards (self:neither, 15.28 ± 0.70 spikes per s; self:other, 16.47 ± 0.81) and allocated rewards to other (15.81 ± 1.16 spikes per s) (both $P > 0.64$, Welch two sample t test), but responded significantly less to neither rewards (10.17 ± 1.23 spikes per s, other versus neither and self versus neither, both $P < 0.005$). Similarly, on cued trials, this neuron preferred other over neither rewards ($P < 0.05$, Welch two sample t test), but did not differentiate between self and other rewards ($P = 0.27$).

Notably, the fact that the solenoid valves controlling juice delivery (including one for neither rewards that only produced clicks) were placed outside the experimental room, as well as the white noise played inside the room, during sessions rules out a simple explanation that other reward–specific (**Fig. 3b**) and shared self/other reward responses (**Fig. 3d**) were merely sensory responses to the sounds of the reward-delivery mechanism.

To contrast population coding of decision and reward information in various conditions, we computed a normalized activity bias between each pair of outcomes, expressed as a proportional modulation in mean firing rates normalized by baseline firing rate. In the ACCg population, the mean normalized activity bias for other over neither rewards (other versus neither) was 0.21 ± 0.10 (s.e.m.), a 21% difference, which was significant ($P < 0.05$, paired t test; **Figs. 3e** and **5a**). Similarly, the bias for self (from self:other) over neither rewards was 0.20 ± 0.12 ($P = 0.09$, paired t test). Notably, the population showed equivalent responses for self rewards (self:other) and other rewards (0.01 ± 0.12, $P = 0.96$, paired t test). On the other hand, it showed a significant bias for self rewards when the actors were presented with a choice between rewarding themselves and recipients compared with when the actors were presented with a choice between rewarding themselves and no one (self:other versus self:neither, 0.17 ± 0.08, $P < 0.05$, paired t test), suggesting that ACCg is particularly sensitive to a reward context involving an option to reward another individual. Thus, the ACCg population showed an equivalent preference for other and self rewards, and preferred both over neither rewards.

On cued trials, however, a notably different pattern emerged. The population responded strongly to self rewards, but barely responded to other rewards (0.59 ± 0.32, $P = 0.07$, paired t test; **Fig. 3e**). Furthermore, the population responded no differently to other and neither rewards (0.22 ± 0.14, $P = 0.14$, paired t test).

Taken together, these results indicate that ACCg, as a population, encodes both giving and receiving rewards. At the population level, neuronal activity selective for allocating rewards to another individual was specific to active decisions (**Fig. 3e**), similar to what has been reported by functional magnetic resonance imaging of human ventral striatum during voluntary versus forced charitable donations[25]. The confluence of neurons selectively responsive to self, other and both (self and other) rewards in ACCg suggests that this area contains the information necessary to mediate the vicarious reinforcement processes that appear to motivate actors to give to recipients.

Figure 4a shows a typical ACCs neuron that fired more strongly preceding other and neither rewards than self rewards. On choice trials, this neuron discharged more strongly when the actor monkey chose not to reward himself (other rewards, 19.64 ± 2.15 spikes per s; neither rewards, 18.19 ± 2.03) compared with when he chose to reward himself directly (self:neither, 10.31 ± 0.86 spikes per s; self:other, 9.79 ± 0.81) (all $P < 0.001$, Welch two sample t test). The example neuron responded equivalently to self rewards in self:other and self:neither contexts ($P = 0.66$, Welch two sample t test), and responded equivalently to other and neither rewards ($P = 0.62$), consistent with encoding 'foregone' rewards. On cued trials, this neuron responded equivalently to other and neither rewards ($P = 0.39$, Welch two sample t test), but responded less to self rewards (both $P < 0.005$), resembling the responses to active decisions.

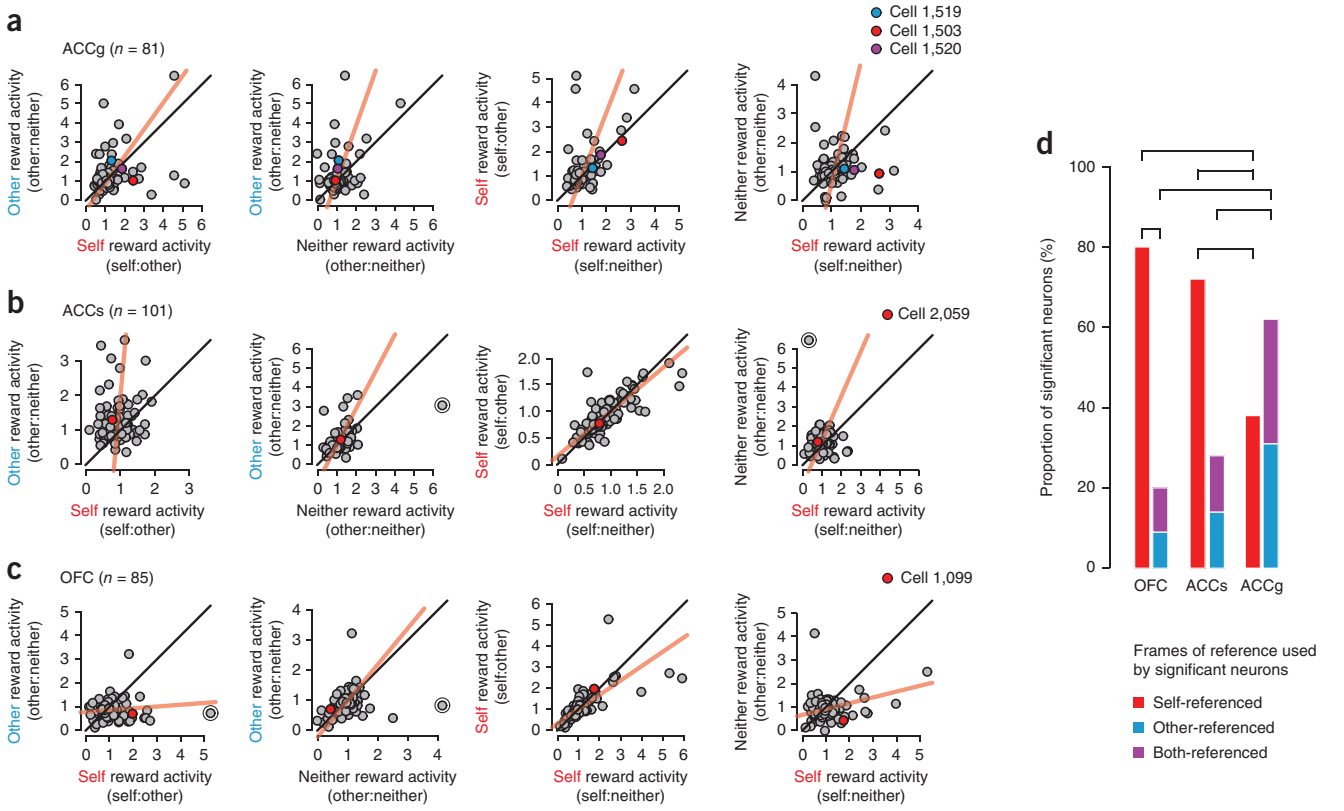

Figure 5 Population biases for self, other and neither rewards. (**a**–**c**) Scatter plots show mean normalized reward epoch responses (proportion of modulation relative to baseline) of individual neurons (from left to right) between self (self:other) and other rewards, between other and neither rewards, between self rewards from self:neither and self:other contexts, and between self (self:neither) and neither rewards for ACCg (**a**), ACCs (**b**) and OFC (**c**) populations. Regression lines (type II) are shown in red (the circled data points are excluded from the regression). Unity lines are shown in black. The example neurons from **Figures 3** and **4** are indicated on the scatter plots. (**d**) Proportion of neurons (out of significantly classified neurons) from OFC, ACCs and ACCg using self-referenced, other-referenced and both-referenced frames to represent reward outcomes. Inset shows color codes used in the bar graph. Bars indicate significant differences in proportions ($P < 0.05$, χ^2 test).

Figure 4b shows a typical OFC neuron that preferentially encoded juice rewards received by the actor. On choice trials, this neuron discharged substantially more for self rewards than for the alternatives on both self:neither and self:other trials. Activity for self rewards did not differ between the two self reward contexts (7.00 ± 0.47 and 7.03 ± 0.46 spikes per s, respectively; $P = 0.97$, Welch two sample t test), but it exceeded the cell's activity for other and neither rewards (3.06 ± 0.40 and 1.85 ± 0.42 spikes per s, respectively; both $P < 0.0001$). On cued trials, this neuron responded most strongly to self rewards than to both other and neither rewards (both $P < 0.0001$, Welch two sample t test), but it did not respond differently between other and neither rewards ($P = 0.25$) (**Fig. 4b**).

The ACCs population showed a strong and equivalent response bias for foregone rewards (self versus other, activity bias = 0.31 ± 0.07; self versus neither, activity bias = 0.25 ± 0.08, both $P < 0.005$, paired t test; **Figs. 4c** and **5b**). The population did not differentiate other from neither rewards (0.06 ± 0.06, $P = 0.31$, paired t test). Unlike ACCg, the population did not respond differentially to self:other and self:neither contexts (differed by 0.003 ± 0.02, $P = 0.90$, paired t test). We found similar patterns on cued trials: responses to self rewards were substantially reduced compared with other rewards (0.19 ± 0.09, $P < 0.05$, paired t test) and neither rewards (0.18 ± 0.10, $P < 0.08$) (**Fig. 4c**). These results indicate that, during social interactions, ACCs neurons predominantly signal foregone rewards.

The OFC population predominantly encoded self rewards compared with other and neither rewards. The bias for self over other rewards was 30% (0.30 ± 0.09, $P < 0.005$, paired t test). For self versus neither rewards, the bias was also significant (0.17 ± 0.08, $P < 0.05$, paired t test; **Figs. 4d** and **5c**). Population activity for other and neither rewards did not differ (0.08 ± 0.06, $P = 0.20$, paired t test; **Figs. 4d** and **5c**). Unlike ACCg, the population did not respond differentially to self:other and self:neither contexts (differed by 0.06 ± 0.07, $P = 0.39$, paired t test). On cued trials, the self reward bias was not present compared with other rewards (0.19 ± 0.16, $P = 0.24$, paired t test) and was only weakly present over neither rewards (0.26 ± 0.15, $P < 0.08$). On cued trials, the population did not distinguish other rewards from neither rewards ($P = 0.33$, paired t test; **Fig. 4d**). These results indicate that OFC neurons predominantly encode rewards received by the actors and that this information was encoded more faithfully during active decision-making.

Neuronal reference frames for social decisions

Neuroimaging and scalp-recording studies in humans can only study neuronal activity at an aggregate level. Our single-unit recording data therefore provide a unique opportunity to quantify the frame of reference in which individual neurons in ACCg, ACCs and OFC encode social decisions. To do this, we classified cells from each area on the basis of an analysis of variance (ANOVA) of neuronal activity of individual neurons with reward outcome (self, other or neither), trial type (choice or cued) and reward magnitude (small, medium or large) as factors (Online Methods). Reward epoch responses differed

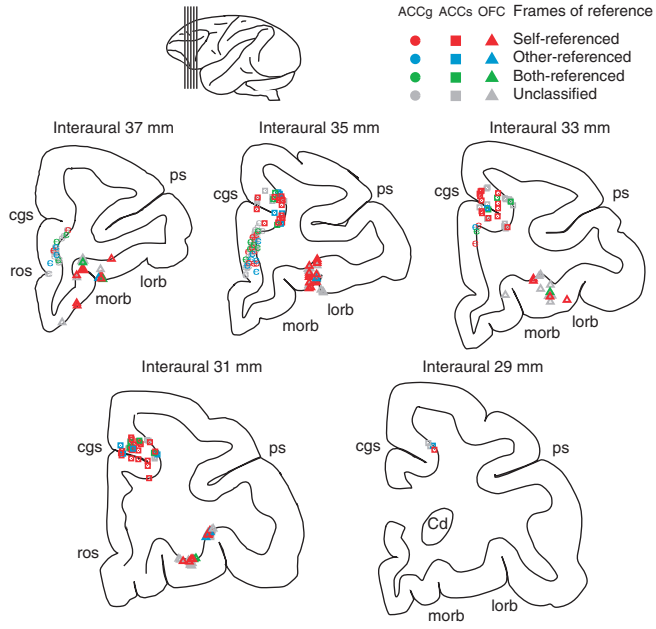

Figure 6 Anatomical projections of recorded locations of all ACCg, ACCs and OFC cells. Recording sites were transformed from chamber coordinates into interaural coordinates. The interaural coordinates of individual cells from both monkeys were then projected onto standard stereotaxic maps of rhesus monkeys[50], with a 2-mm interaural spacing in the anterior-posterior dimension. Cells are shown on coronal slices and color-coded for the types of frames of reference used, as specified in **Supplementary Table 1** (see box). The lateral view of the brain (inset) shows the locations of the coronal sections. Cd, caudate; cgs, cingulate sulcus; lorb, lateral orbitofrontal sulcus; morb, medial orbitofrontal sulcus; ps, principal sulcus; ros, rostral sulcus.

significantly ($P < 0.05$) for a large number of neurons from all areas in a manner that depended on reward outcome (ACCg, 57%; ACCs, 72%; OFC, 57%), trial type (ACCg, 36%; ACCs, 52%; OFC, 45%) and reward volume (ACCg, 12%; ACCs, 25%; OFC, 24%) (**Supplementary Table 1**). Furthermore, we observed marked similarities in reward outcome coding across the choice/cue and reward epochs (**Supplementary Fig. 4**).

On the basis of the statistical significance of the ANOVA during the choice/cue and reward epochs, we identified individual neurons as self-referenced (modulation referenced to self rewards, preferring either self or foregone rewards), other-referenced (modulation referenced to other rewards), both-referenced (modulation referenced to both self and other rewards, but not neither rewards) or unclassified (Online Methods). We considered the proportion of different cell types among the classified neurons based on this scheme. In OFC, 80% ($n = 36$ of 45 neurons) were self-referenced, whereas only 9% (4 of 45) were other-referenced and 11% (5 of 45) were both-referenced (both $P < 0.0001$, χ^2 test; **Fig. 5d**). In ACCs, 72% (51 of 71) were self-referenced, whereas only 14% (10 of 71) were other-referenced and 14% (10 of 71) were both-referenced (both $P < 0.0001$, χ^2 test; **Fig. 5d**). In contrast, ACCg contained similar proportions that were self-referenced (38%, 12 of 32), other-referenced (31%, 10 of 32) and both-referenced (31%, 10 of 32) ($P > 0.79$, χ^2 test; **Fig. 5d**). Notably, ACCg contained a significantly higher proportion of neurons (>60%) that were sensitive to the reward outcome of the recipient monkey (other-referenced and both-referenced) than either OFC or ACCs (both $P < 0.005$, χ^2 test; **Fig. 5d**). ACCg also contained a significantly smaller proportion of self-referenced neurons than either OFC or ACCs (both $P < 0.005$, χ^2 test). Finally, we found similar results when we repeated the analysis and included trial-by-trial choice reaction times as covariates (**Supplementary Fig. 5**).

To test whether different neuronal frames of reference (self-, other- and both-referenced) were anatomically segregated, we used principal component analysis on recording coordinates to identify the major axis with the largest dispersion in three-dimensional space. We then projected neurons to that axis to test differential distributions in individual monkeys separately (**Fig. 6**). We did not observe any systematic anatomical clustering among different frames of reference; self-, other- and both-referenced neurons in ACCg, ACCs and OFC were intermingled (all $P > 0.56$, Wilcoxon rank sum test).

Next, we examined whether differential encoding of self, other and neither rewards was also present before making a decision. We found very little evidence for systematic signals early in the trial just after target onset (50–250 ms after target onset). In ACCg, only zero, three and one cells were classified into self-, other- and both-referenced classes, with only 12% of neurons showing significant effect of reward type. In ACCs, only one, two and three cells belonged to each category, with only 22% of the neurons showing significant reward type effects. Similarly, in OFC, only two, two and four cells belonged to each category, with only 28% of the neurons showing significant reward type effects. Thus, in our reward allocation task, signals in ACCg, ACCs and OFC appear to emerge around the time of choice and reward delivery.

When we examined the reward magnitude sensitivities of individual neurons, we found the population in ACCs to be most sensitive (**Supplementary Figs. 6** and **7**). Furthermore, signal-to-noise in neuronal responses to specific reward outcomes were largely consistent with the preferred neuronal encoding scheme in each region (**Supplementary Fig. 8**). None of our findings were driven by whether or not actors looked at recipients (**Supplementary Fig. 9**).

Finally, we examined whether session-to-session variation in prosocial tendencies on other:neither trials (**Fig. 2c**) could be explained by variability in the responses of ACCg neurons, the population most sensitive to other's rewards. We split recording sessions on the basis of actors' choices on other:neither into two categories: more prosocial (higher other over neither choices relative to the median preference index) and less prosocial (lower other over neither choices relative to the median preference index). Actors tended to be more prosocial on recording sessions when other-referenced and both-referenced ACCg neurons showed less variability in spiking during the reward epoch ($P < 0.05$, bootstrap test; **Fig. 7a**).

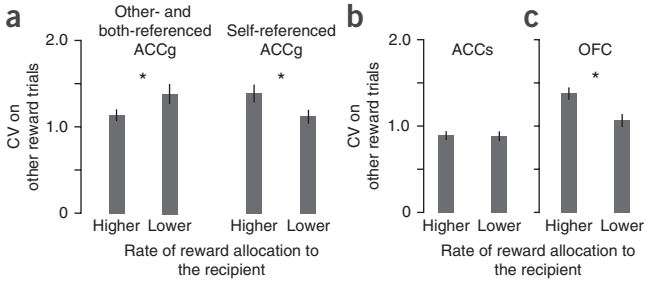

Figure 7 Prosocial behavior and the fidelity of neuronal responses on other:neither trials. (**a**) ACCg. (**b**) ACCs. (**c**) OFC. Coefficients of variation in firing rate (CV; Online Methods) during the reward epoch on other reward trials are plotted as a function of whether actors were more or less prosocial on other:neither trials on the basis of median split (higher: preference index greater than median; lower: preference index less than median). *$P < 0.05$, bootstrap test.

In contrast, we found that self-referenced ACCg neurons generated more variable responses during the reward epoch in which actors were more prosocial ($P < 0.05$, bootstrap test). ACCs neurons did not show any systematic relationship between response variance and behavior ($P = 0.47$, bootstrap test; **Fig. 7b**). Notably, OFC neurons showed a similar pattern as self-referenced ACCg neurons ($P < 0.005$, bootstrap test; **Fig. 7c**). These findings suggest a strong link between prosocial behavior and the fidelity of social reward signals carried by those neurons that incorporate the experience of others into their responses. This could be a result of enhanced attention to the recipient or other processes known to influence signal-to-noise in cortical neurons.

DISCUSSION

Our findings strongly endorse the hypothesis that distinct frontal regions contribute uniquely to social decisions by differentially processing decision outcomes with respect to actors (self) and their partners (other). The finding that OFC neurons selectively encode self reward is consistent with previous results implicating this area in representing the subjective value of rewards[12,13], but extend those results by demonstrating that such value signals are encoded egocentrically. Encoding of foregone rewards by ACCs neurons, on the other hand, is consistent with previous data implicating this area in error monitoring and behavioral adjustment[35–37]. For example, foregone reward signaling by ACCs might be used to learn from observation, rather than direct experience, and adjust ongoing behavior during social interactions. Furthermore, mirroring of self and other rewards by ACCg neurons is consistent with previous studies linking this area to specifically social functions, such as shared experience and empathy[38].

Our findings are consistent with those of a previous study examining the effects of lesions in these same brain regions (Online Methods), which found that ACCg, but not OFC or ACCs, contributes causally to the use of visual social information to guide behavior[9]. Specifically, ACCg lesions completely abolished typical hesitation to retrieve food when confronted with social stimuli[9]. Our findings also agree with previous findings that lesions in ACCs impair the use of reward history to guide decisions adaptively[10]. The differences between ACCs and ACCg that we observed support and extend the finding that learning from experience is mediated by ACCs, whereas learning from feedback from another individual is mediated by ACCg[8]. Specifically, in a learning task in which human subjects monitored their history of correct responses as well as the advice given to them by a confederate, blood oxygen level–dependent (BOLD) activation in ACCs tracked reward learning rate, whereas BOLD activation in ACCg tracked social learning rate based on advice from the confederate[8]. In our study, we propose that ACCs tracked foregone rewards relative to self, whereas ACCg tracked reward outcomes of another individual in a more complex manner.

Notably, the ACCg population also responded more strongly when monkeys chose self reward when the alternative was allocating reward to the other monkey compared with the response when monkeys chose self reward when the alternative was rewarding no one. In contrast, neither the OFC neuronal population response nor the ACCs neuronal population response was sensitive to social context when monkeys rewarded themselves. Sensitivity to social context in ACCg endorses a specialized role for this area in computing social decisions, even when one acts selfishly.

It is worthwhile to note that a small number of ACCs and OFC neurons, although much less in proportion compared with ACCg (**Fig. 5d**, **Supplementary Table 1** and **Supplementary Fig. 5**), were classified as either other- or both-referenced. This observation supports the idea that a small number of ACCs and OFC neurons do carry information about rewards allocated to another individual. What is notable is that the majority of OFC and ACCs neurons (80% and 72%, respectively) did not carry such other-regarding information (other- or both-referenced), whereas the majority of ACCg neurons did (62%). This endorses a fundamentally social role for neurons in ACCg.

A prior study showed that OFC neurons modulate their activity when a monkey receives juice reward together with another individual[39], suggesting that value signals in OFC are sensitive to social context. In that study, OFC neurons responded differentially as a function of whether the subject monkey received juice rewards alone or together with another monkey[39]. Our current study builds on and extends those findings in three important ways. First, we used a free-choice task that allowed us to infer the subjective value of rewards delivered to self, other and no one. Notably, even in a social context, OFC neurons were selective for self reward, the most preferred outcome. Second, we compared the responses of OFC neurons to responses of neurons in ACCg and ACCs recorded in identical task conditions, allowing us to examine regional differences in the encoding of social reward information in primate frontal cortex. Third, when we compared responses of ACCg neurons on free-choice and cued trials, we found that responses to rewards delivered to the recipient monkey were largely absent when actors passively observed the event rather than actively choosing it. Taken together, these findings indicate that social context can affect the encoding of reward information in all three areas; OFC appears to evaluate personally experienced rewards, ACCs evaluates reward information that is not directly experienced, and ACCg multiplexes information about the direct experience of reward and vicarious reinforcement experienced by allocating reward to another individual.

It is noteworthy that ACCs neurons showed much less modulation by actors' received reward outcomes compared with OFC neurons, as ACCs neurons often show substantial modulation to received reward in nonsocial settings[11]. ACCg, on the other hand, contains neurons that compute reward signals in both other and self frames of reference. Together, our findings suggest that, as in sensory and motor systems[40], identifying the frames of reference in which reward outcomes are encoded may be important for understanding the neural mechanisms underlying social decision-making[8].

Accumulating evidence endorses a special role for the medial-frontal cortex in representing information about another individual[8,41–44]. For instance, perceived similarity while observing others is correlated with hemodynamic response in the subgenual ACC[44]. Furthermore, a group of neurons in the primate medial-frontal cortex selectively responds to observing actions performed by other individuals[41]. Such other-referenced signals, however, are not limited to the medial wall of the frontal cortex. Neurons in the dorsolateral prefrontal cortex (DLPFC) track the behavior of a computer opponent in an interactive game[45], and BOLD responses in DLPFC and ventromedial prefrontal cortex during observational learning track observed action and observed reward prediction errors, respectively[46]. In addition, BOLD activity in anterior frontal areas tracks preferences to donate to charity[24]. Brain networks involved in mentalizing[47], vicarious pain perception[48] and empathy[49] therefore seem to be critical for mediating social interactions, suggesting that other-regarding cognition is orchestrated by a distributed network of frontal cortical areas.

Social and emotional behaviors are highly idiosyncratic among individuals. Understanding the neural mechanisms that drive such

individual differences remains one of the most pressing issues in neuroscience. We hypothesize that the differential activation of neurons in ACCg, ACCs and OFC contribute to individual and, perhaps, species differences in social function.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Supplementary information is available in the online version of the paper.

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AUTHOR CONTRIBUTIONS

S.W.C.C. and M.L.P. designed the study and wrote the paper. S.W.C.C. and J.-F.G. performed the experiments and S.W.C.C. analyzed the data.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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ONLINE METHODS

General and behavioral procedures. All procedures were approved by the Duke University Institutional Animal Care and Use Committee, and were conducted in compliance with the Public Health Service's Guide for the Care and Use of Laboratory Animals.

Two actor (MY and MO) and five recipient monkeys (*Macaca mulatta*) participated. For all monkeys, a sterile surgery was performed to implant a head-restraint prosthesis (Crist Instruments) using standard techniques[11]. Six weeks after surgery, monkeys were trained on a standard, center-out, oculomotor task for liquid rewards. Actor monkeys were then trained on the reward-allocation task (**Fig. 1**) in the presence of a recipient. Subsequently, a second surgery was performed on actors to implant a recording chamber (Crist) providing access to the ACCs, ACCg and OFC. All surgeries were performed under isoflurane anesthesia (1–3%, vol/vol), and the recording chambers were regularly cleaned, treated with antibiotics and sealed with sterile caps.

Horizontal and vertical eye positions were sampled at 1,000 Hz using an infrared eye monitor camera system (SR Research Eyelink). Stimuli were controlled by PsychToolBox and Matlab (MathWorks). Actors and recipients sat in primate chairs (Crist), 100 cm from one another at a 45° angle (**Fig. 1a**). Actors (both males) and recipients (four males, one female) were unrelated and were not cagemates. Different pairs were selected depending on the availability of recipient monkeys. Actors were housed in a colony with 12 other male rhesus macaques, some of which were pair-housed. All of the male monkeys resided in this colony room, and the one female monkey resided in the adjacent colony room with other females. Of the total seven actor-recipient pairs that we tested, the actor monkey was dominant over the recipient in six cases. Furthermore, three pairs could be classified as 'more familiar' with one another because their cages faced each other, as defined previously[33]. Based on these relationships, we would expect a mixture of prosocial and competitive preferences, as we previously found that dominant actors are slightly less competitive than subordinates, but pairs in which the actor is less familiar with the recipient are slightly less prosocial than when they are more familiar.

In the experimental setup, each monkey had his own monitor, which displayed identical visual stimuli. Both the actor and recipient monkeys had their own tube from which juice drops were delivered. To prevent monkeys from forming secondary associations of solenoid valve clicks or the sound of the recipient drinking the juice reward with respect to different reward types, the solenoid valves that delivered the juice rewards were placed in another room and white noise was also played in the background. Experimenters were unable to hear solenoids anywhere inside the recording room. Our control of the acoustic environment explicitly rules out a simple explanation that both-referenced reward encoding found in ACCg is a product of such secondary sensory associations. Critically, a separate solenoid (also placed in another room) was designated for neither rewards; it produced clicks, but delivered no fluid.

The face region of the recipient, with respect to the gaze angle of the actor (horizontal and vertical eye positions), was determined empirically before the experiments. The frequency with which actors looked at recipients was computed from number of gaze shifts to the recipient's face (±8.5° from the center of the face)[33,34]. We used a large window to capture gaze shifts that were brief in duration and large in magnitude and often directed at varying depths (for example, eyes and mouth; **Fig. 1a**).

Monkeys performed the task to obtain drops of cherry- or orange-flavored juice. Actors began a trial by shifting gaze (±2.5°) to a central stimulus (0.5° × 0.5°), and maintained fixation (200 ms). For 219 single-unit sessions, the reward magnitude at stake (0.1–2.4 ml) on each trial was cued by the position of a horizontal bisecting line (200 ms), indicating the percentage of the maximum possible volume. There were two kinds of trials, termed choice trials and cued trials. Following a variable delay (300, 500 and 700 ms), choice and cued trials were presented at equal probabilities, randomly interleaved. On choice trials, two visual targets (4° × 4°) appeared at two random locations 7° eccentric in the opposite hemifield. Actors shifted gaze to one target (±2.5°) to indicate a choice in the maximum allowed time of 1.5 s (from stimulus onset). The pair of stimuli appearing on a given trial was drawn from the set of three stimuli (**Fig. 1b**), pseudorandomly selected. On cued trials, actors maintained fixation (±2.5°) while a cue (4° × 4°) appeared centrally (500 ms). Cues indicating rewards for the actor, recipient or neither monkey occurred with equal frequency, pseudorandomly determined (**Fig. 1b**). Reward onset was followed by a 0–900-ms delay from the time of either making a choice or cue offset. Actors were free to look around during this delay and for 1 s after reward delivery. Reward delivery was followed by an intertrial interval of 700, 1,000 or 1,300 ms. After making an error (see below), both monkeys received visual feedback (a white rectangle, 10° × 10°) followed by a 5-s time out before the next trial.

Recording procedures. All recordings were made using tungsten electrodes (FHC). Single electrodes were lowered using a hydraulic microdrive system (Kopf Instruments or FHC). Single-unit waveforms were isolated and action potentials were collected using a 16-channel recording system (Plexon).

To guide the placement of recording tracks and localize recording sites, we acquired structural magnetic resonance images (MRI; 3T, 1-mm slices) of each actor's brain. Detailed localizations were made using Osirix viewer. In addition to MRI guidance, we confirmed that electrodes were in ACCg, ACCs or OFC by listening to gray matter– and white matter–associated sounds while lowering the electrodes. ACCg neurons were recorded from Brodmann areas 24a, 24b and 32, ACCs neurons (dorsal and ventral banks) were recorded from 24c and 24c', and OFC neurons were recorded from 13m and 11 (based on standard anatomical references[51,52]; **Figs. 3a** and **6**).

Single-unit recordings were made from two actor monkeys while each was engaged in a reward-allocation task with a recipient monkey in 267 sessions. A total of 81 ACCg neurons (MY, 45; MO, 36), 101 ACCs neurons (MY, 39; MO, 62) and 85 OFC neurons (MY, 46; MO, 39) were included in the study. Neurons were selected for recording based solely on the quality of isolation. For a small subset of the data (18%; ACCg, 0%; ACCs, 25%; OFC, 27%), data were collected in a task with a fixed reward size (typically 1.0 ml per successful trial; identical to **Fig. 1d** except without the magnitude cue). For the majority of the cells (82%, $n = 219$), data were either collected in a task with the magnitude cue (ACCg, 100%, $n = 81$; ACCs, 60%, $n = 61$; OFC, 42%, $n = 36$; **Fig. 1d**) or both with and without the magnitude cue (that is, two or more consecutive blocks per cell; ACCg, 0%; ACCs, 15%, $n = 15$; OFC, 31%, $n = 26$). We combined the two types of data in our analyses unless otherwise specified.

Data from each cell consisted of firing rates during 440 ± 13 (±217) (median ± s.e.m. (±s.d.)) trials. A trial was considered incomplete if the monkey failed to choose a target on choice trials (choice-avoidance error) or to maintain fixation after cue onset on cued trials (forced-choice avoidance error). Such trials were not included in the neural analysis. The monkeys performed the task well, as evidenced by a high percentage of correct trials even on trials in which they did not receive juice reinforcement (**Fig. 2a**).

Data analysis. Choice preference indices were constructed as contrast ratios[33,34].

$$\text{Preference Index} = \frac{R_A - R_B}{R_A + R_B} \quad (1)$$

R_A and R_B were the frequency of making particular choices. For self:other trials, R_A and R_B were number of choices to reward other and self, respectively. For other:neither trials, R_A and R_B were number of choices to reward other and neither, respectively. Finally, for self:neither trials, R_A and R_B were number of choices to reward neither and self, respectively. Indices therefore ranged from −1 to 1, with 1 corresponding to always choosing to allocate reward to other on other:neither trials and self:other trials, and always choosing not to reward self on self:neither trials. An index of −1 corresponds to the opposite, generally stated as choosing not to allocate reward to the other monkey or choosing to reward oneself. Values of 0 indicate indifference. For constructing neuronal preferences, we simply substituted the choice frequency with neuronal firing rates associated with making specific decisions. Response times, the time from the onset of choices to movement onset, were computed using a 20° s^{-1} velocity threshold criterion[33,34].

Spike rates were computed during the reward epoch (50–600 ms from reward onset) as well as the choice/cue epoch (−100–300 ms from making a choice or cue offset). For the population analyses, we normalized reward firing rates to the average baseline rates for each reward outcome (300-ms interval before fixation onset). Using marginally different time windows and different normalization methods all resulted in similar conclusions. Coefficients of variation were

calculated for each neuron on the basis of the s.d. (σ) and mean (μ) using the spike rates (spikes per s) from the reward epoch:

$$\mathrm{CV} = \frac{\sigma}{\mu} \quad (2)$$

In OFC and ACCs populations, the two self rewards (that is, self rewards chosen from self:neither and self:other trials) were largely indifferent (**Figs. 4** and **5b**,**c**), and we combined them by taking means for the coefficient of variation analysis. In contrast, the population of ACCg neurons responded more strongly to self rewards obtained from a social context (self:other) compared with when there was no reward stake for the other monkey (self:neither); thus, we considered the two self rewards separately in ACCg (see **Figs. 3** and **5a**).

ANOVA was used to classify the reward response selectivity of individual neurons from each area and performed per individual cells. Two-factor ANOVA was used to classify the selectivity of reward outcome (self, other or neither) and trial type (choice or cued) for all neurons. Three-factor ANOVA was used to classify the selectivity of reward volume (binned into small, medium, large) for the 82% of cells from all areas that were collected in the task with a magnitude cue. Statistical significance for each reward type was computed by Tukey HSD test. Finally, we excluded three OFC cells when our analyses involved using the data from neither rewards because these cells were recorded on very rare sessions in which the monkeys either never chose the neither reward option or did so fewer than four times. Across all analyses, using slightly different epoch durations for neuronal data analyses led to similar results.

Classification of cell types by significant reward specificity. Based on Tukey HSD tests from the one-way ANOVA on reward outcome (self, other, or neither) for both the choice/cue epoch and reward epoch responses, we classified cells into the following categories: self-referenced, other-referenced, both-referenced and unclassified. These categories do not imply functional roles, but indicate that firing rates were significantly different based on reward outcomes. We refer to a neuron as self-referenced if the responses of the neuron were significantly different ($P < 0.05$) between self and other rewards as well as between self and neither rewards, but not different between other and neither rewards. We refer to a neuron as other-referenced if the responses of the neuron showed significant differences in firing rates between self and other rewards as well as between other and neither rewards, but not different between self and neither rewards. Finally, we refer to a neuron as both-referenced if the responses of the neuron showed significant differences in responses between self and neither rewards as well as other and neither rewards, but not different between self and other rewards. Neurons that did not fall into one of these categories were considered as unclassified. Applying slightly different criteria or differently configured ANOVA did not change the overall proportional trends of these classes.

Reward magnitude analysis. We examined reward magnitude modulation in 219 neurons (that is, 82% of all neurons collected with the magnitude cue; 81 ACCg, 76 ACCs and 62 OFC neurons). We performed a linear regression on the activity (spikes per s) of individual neurons across unbinned reward sizes. We fit the data using the reward epoch activity separately for self, other and neither reward outcomes and obtained fitted slopes (that is, reward magnitude sensitivity in spikes per s per ml) for each reward outcome. For examining the relationship between the reward magnitude sensitivity across actors' received and foregone reward outcomes, we compared the average signed slopes from all received rewards (self rewards on choice and cued trials) and all foregone rewards (other and neither reward on choice and cued trials) in individual neurons.

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Inhaled oxytocin amplifies both vicarious reinforcement and self reinforcement in rhesus macaques (*Macaca mulatta*)

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People attend not only to their own experiences, but also to the experiences of those around them. Such social awareness profoundly influences human behavior by enabling observational learning, as well as by motivating cooperation, charity, empathy, and spite. Oxytocin (OT), a neurosecretory hormone synthesized by hypothalamic neurons in the mammalian brain, can enhance affiliation or boost exclusion in different species in distinct contexts, belying any simple mechanistic neural model. Here we show that inhaled OT penetrates the CNS and subsequently enhances the sensitivity of rhesus macaques to rewards occurring to others as well as themselves. Roughly 2 h after inhaling OT, monkeys increased the frequency of prosocial choices associated with reward to another monkey when the alternative was to reward no one. OT also increased attention to the recipient monkey as well as the time it took to render such a decision. In contrast, within the first 2 h following inhalation, OT increased selfish choices associated with delivery of reward to self over a reward to the other monkey, without affecting attention or decision latency. Despite the differences in species typical social behavior, exogenous, inhaled OT causally promotes social donation behavior in rhesus monkeys, as it does in more egalitarian and monogamous ones, like prairie voles and humans, when there is no perceived cost to self. These findings potentially implicate shared neural mechanisms.

social decision-making | neuropeptide | other-regarding preference | social gaze

Oxytocin (OT) (1) is a mammalian neurosecretory hormone, synthesized by hypothalamic neurons, which regulates the hypothalamic-pituitary-adrenal axis (2). The most well-understood role of OT in mammals is in female reproduction, with peripheral OT influencing parturition and lactation (3), and central OT affecting mother-offspring bonding and recognition (4, 5). More recently, OT has been found to influence nonparental social behavior in a species-specific manner. For example, OT promotes pair-bonding between males and females in monogamous prairie voles (*Microtus ochrogaster*) (6, 7) but can also increase aggression (i.e., mate-guarding behavior) and decrease social interaction among females after brief exposure to a male (8). In humans, OT also influences more complex forms of social behavior and cognition (9–14). For example, inhaled OT enhances trusting behavior toward other individuals in economic games, potentially by suppressing aversion to betrayal risk (15), and promotes cooperation within groups (16). However, inhaled OT also provokes cultural and racial biases (17). OT inhalation also enhances sensitivity to the experiences of others by promoting vicarious reward and empathic pain (10, 18, 19). Recently, OT-mediated processes have been implicated in disorders attended by dysfunctional social behavior, including autism, fragile X syndrome, and schizophrenia (19–22). Notably, OT treatment improves social skills in individuals with autism (21, 23, 24), a spectrum of disorders with marked deficits in sensitivity to what happens to others, including impairments in understanding and responding to social cues (22, 25, 26). Variations in a common oxytocin-receptor allele are linked to autism spectrum disorders and are associated with reduced volume in hypothalamus and anterior cingulate cortex (27).

Despite a growing literature, the mechanisms mediating the influence of OT on sensitivity to what happens to others remain only partially understood (9, 14, 19, 21, 28, 29). OT receptors are localized in multiple regions of the brain, with especially high density in areas implicated in affective and social processing. In prairie voles, OT receptors are densely localized in the amygdala, prelimbic cortex (homologous to the cingulate cortex in primates), and nucleus accumbens of the striatum (30). Recently, it has been shown that OT selectively inhibits a dedicated channel from the central nucleus of the amygdala to periaqueductal gray, ultimately reducing fear-induced freezing behavior in rats (31). Similarly, in humans, inhaled OT influences on social behavior are associated with reduced blood oxygen level-dependent (BOLD) signals in the bilateral amygdala and dorsal striatum (28, 29), consistent with the OT-mediated negative affect processing in the amygdala-cingulate circuits (22). These studies provide evidence that OT influences information processing in neural circuits implicated in emotion and social behavior.

Unlike prairie voles or humans (2, 6, 9–11, 13–16, 30, 32, 33), rhesus macaques (*Macaca mulatta*) live in large, hierarchical social groups with promiscuous mating and uniparental female care of offspring. Precisely how OT might influence social cognition in animals with this type of social structure and mating system, if at all, remains unknown. To answer this question, we capitalized on a recent finding by our group showing that rhesus macaques are sensitive to the rewards experienced by others, and this vicarious reinforcement is sufficient to motivate them to work to reward another monkey when the alternative is delivering reward to no one (34). We found that inhaling OT increased OT levels in cerebral spinal fluid (CSF), demonstrating transnasal penetration into the CNS. Roughly 2 h after OT-inhalation and onward, donor monkeys selectively increased the frequency of choosing an option resulting in reward to an adjacent, visible monkey, when the alternative was rewarding no one. In the same context, OT also increased the frequency that donors looked at the recipient monkey and prolonged choice response times. In contrast, up to about 2 h postinhalation, OT increased selfish decisions when the donors had the option to reward self over the other monkey. These findings invite the hypothesis that OT boosts internal vicarious reinforcement signals in a context-dependent manner in neural circuits homolo-

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gous to those mediating these processes in humans. Our results demonstrate that OT mediates other-regarding behavior in nonhuman animals, even in those living in despotic societies with uniparental care.

Results

Donor monkeys (hereafter, "self" or "donor") performed a reward allocation task with an unrelated recipient monkey ("other") (Fig. 1 *A*–*C*) (34). The two monkeys were seated in adjacent primate chairs (Crist), 100-cm apart and at 45° angles to each other. Each monkey viewed his own LCD display, and had a juice-tube positioned in front of his mouth through which reward could be delivered. On each trial, donors chose between two visual shapes, associated with rewarding self, other, or neither. We have previously shown that donors typically prefer the shape delivering reward to other over neither (34). This preference is enhanced by greater familiarity between the two monkeys, and is abolished if the recipient monkey is replaced with a juice collection bottle, thus demonstrating the fundamentally social nature of the task (34).

For each session, we intranasally (35) delivered 25 international units (IU) of OT or saline, on alternating days, to two males using a pediatric nebulizer 30 min before performing the reward allocation task. A session composed of multiple reward allocation trials after either OT or saline administration occurred on each day (*Methods*). Data from a total of 12 OT and 10 saline control sessions were collected from two donors (MY and MO) while they engaged in the reward allocation task (Fig. 1 *A*–*C*) with an unrelated recipient monkey (MD). Five OT and three saline sessions were collected from MY, and seven OT and saline sessions each were collected from MO. For statistical power, we present data collapsed across the two donors, unless otherwise stated.

OT inhalation, compared with saline, significantly increased OT concentration in CSF as measured by cervical draws ($P < 0.05$, Welch two-sample t test) (Fig. 1*D*), confirming transnasal penetration into the CNS. Thirty minutes after OT administration, donors began the reward allocation task. For choices between delivering reward to other and neither, OT selectively amplified reward donations to other (Fig. 2). Preference for other increased linearly over time after OT but not after saline (OT: different from 0, $r^2 = 0.26$, $P < 0.0005$; saline: $r^2 = 0.01$, $P = 0.47$, linear regression) (Fig. 2). OT-induced enhancement of prosocial choices was largest in the later half of a given session (i.e., ~110 min after OT administration and ~80 min after task initiation; preference index mean difference between OT vs. saline: 0.17, $P < 0.00001$, Welch two-sample t test) (Fig. 2). Individual donors showed a similar pattern (MY: 0.18, $P < 0.00001$; MO: 0.19, $P < 0.01$). We found a significant difference between the two treatment conditions even when we averaged across the entire duration of the task (mean difference of 0.12, $P < 0.00001$; MY: 0.15, $P < 0.00001$; MO: 0.06, $P < 0.05$, Welch two-sample t test).

In contrast, in the early half of a given session (i.e., up to ~80 min into the task), OT slightly but significantly increased selfish

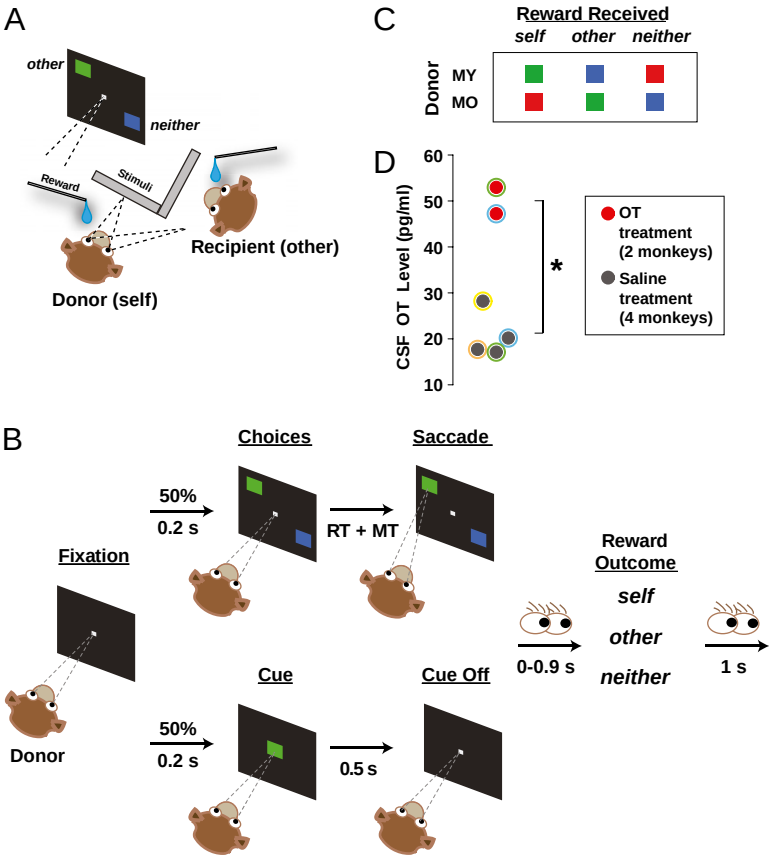

Fig. 1. Reward allocation task. (*A*) Experimental setup. (*B*) Trial sequence. Choice (*Upper*) and cued (*Lower*) trials were randomly interleaved. The eye-gaze cartoons specify the task intervals during which the donors could potentially look at the recipient monkey. MT, movement time; RT, reaction time. (*C*) Stimuli associated with different reward outcomes to donors and recipient, shown separately for the two donors. (*D*) OT concentration in the CSF after intranasal OT (in red) or saline (dark gray). *$P < 0.05$, Welch two-sample t test. Colored outlines on the datapoints represent animal identities.

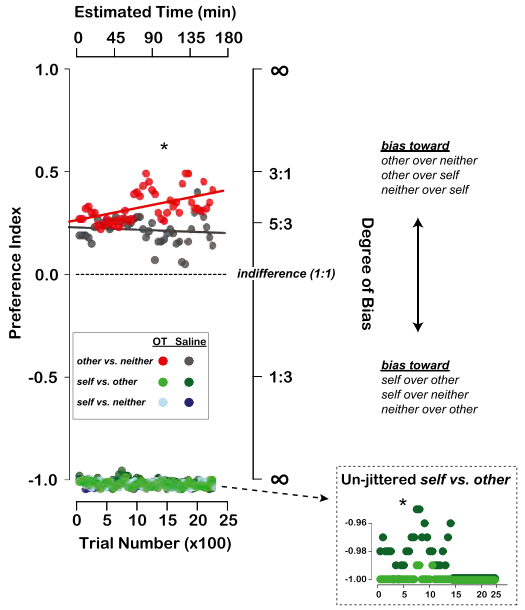

Fig. 2. Intranasal OT promotes both vicarious and self reinforcement. Choice preference index (moving averages of 200 trials per session, 50-trial step) for OT (red) and saline (gray) across all reward options (other vs. neither, self vs. other, and self vs. neither). Datapoints from self vs. other and self vs. neither are jittered along the ordinate for visibility. (*Inset*) Unjittered and magnified data from self vs. other trials. Data from self vs. neither trials were effectively overlapping between the OT and saline conditions, and therefore not shown in an unjittered format. OT, 12 sessions; saline, 10 sessions. Lines show linear regression on other vs. neither trials.

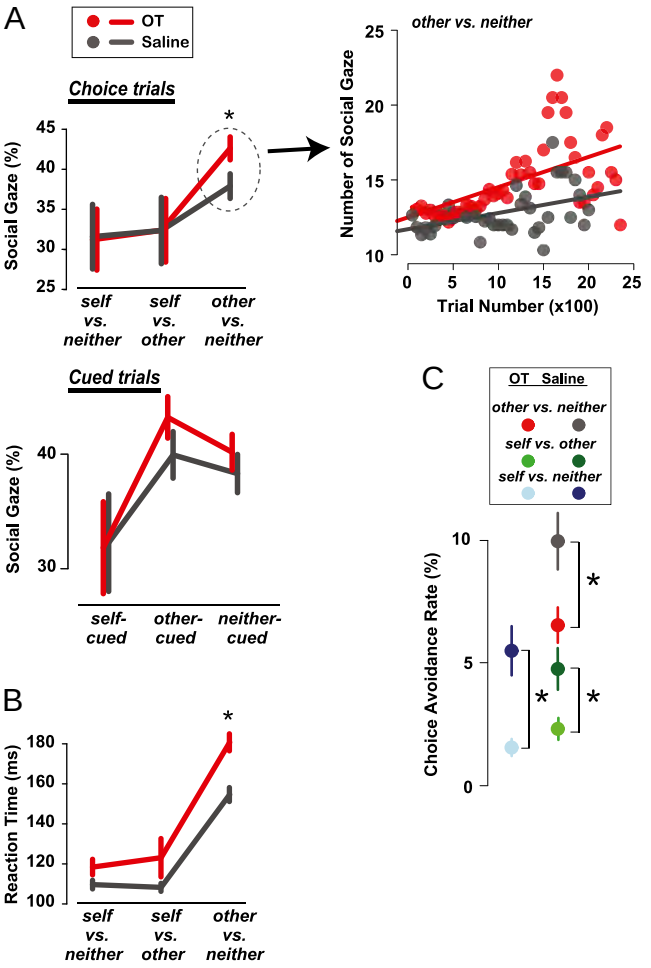

Fig. 3. Intranasal OT enhances attention to the recipient monkey and increases the deliberation time for making donation decisions. (*A*) Gaze to the face of the other monkey after reward delivery. (*Left*) Percentages of gaze shifts to the recipient monkey on choice trials (*Upper*) and cued trials (*Lower*). (*Right*) Number of gaze shifts over the course of each day session for other vs. neither choice trials (moving averages of 200 trials per session, 50-trial step). Lines through the datapoints show linear regressions. (*B*) Response times, measured as saccade onset times following target onset (ms). (*C*) OT reduced choice avoidance [i.e., declining to choose by breaking fixation upon target onset (such as, reward options), which, in the task resulted in a time out for 5 s]. *$P < 0.05$, Welch two-sample t test.

choices on self vs. other trials compared with saline control (mean difference between OT and saline of −0.02, $P < 0.00001$, Welch two-sample t test; *Inset* in Fig. 2 shows unjittered self vs. other trials), but had no effect on self vs. neither trials (mean difference of −0.002, $P = 0.36$). Individual donors showed a similar selfish bias (MY: −0.003, $P < 0.06$; MO: −0.04, $P < 0.00001$). The absence of OT effect on self vs. neither trials might be due to the fact that this context does not involve a potential reward to another monkey, although we cannot rule out the possibility that donors were maximally self-regarding in this context in the absence of OT. Thus, OT robustly enhanced prosocial choices when there was no potential cost to self, but slightly increased selfish choices when there was potential for direct self reward.

Donor monkeys often shift gaze to the recipient monkey after making a choice, and this attention to the recipient is enhanced after prosocial choices compared with selfish choices (34). OT further enhanced this overt other-oriented attention to the recipient after donors made a decision on other vs. neither trials (Fig. 3*A*) (OT vs. saline: mean difference of 4.70%, $P < 0.05$, Welch two-sample t test). In contrast, we did not observe any effects of OT on donor's attention to the recipient when direct self reward was involved (self vs. neither: mean difference of −0.36%, $P = 0.95$; self vs. other: 0.03%, $P = 0.99$) (Fig. 3*A*). We also found that donors looked more frequently to the recipient when rewards were delivered to him compared with when rewards were delivered to self, even on cued trials in which rewards were delivered by computer without any action by donors (gaze frequency on self-cued vs. other-cued trials: OT, $P < 0.005$; saline: $P = 0.05$) (Fig. 3*A*). However, OT did not modulate this difference in social attention on cued trials (all comparisons $P > 0.23$, Welch two-sample t test) (Fig. 3*A*), suggesting that OT enhances other-oriented attention selectively following prosocial decisions rather than in response to anything happening to the other monkey (i.e., after active choices on other vs. neither trials). As in the other-oriented choice preference, attention to the recipient monkey also increased linearly over time after OT (slope significantly different from 0: $r^2 = 0.31$, $P < 0.00001$, linear regression) (Fig. 3*A*, *Right*). The frequency of looking at the recipient monkey in the saline control also increased over the course of the session ($r^2 = 0.19$, $P < 0.005$), but with a significantly lower rate of rise than the OT condition (differences in OT and saline slopes greater than zero: $P < 0.005$, permutation test) (Fig. 3*A*). This finding suggests that OT enhances the intensity of vicarious reinforcement in part by modulating attentional mechanisms.

We also examined the time required by monkeys to render a decision. Response times in the reward allocation task are generally slower when donor monkeys choose between delivering reward to other vs. neither, compared with when self reward is involved (34). OT selectively prolonged response times on other vs. neither trials (mean difference between OT and saline of 26.0 ms, $P < 0.00001$, Welch two-sample t test) (Fig. 3*B*), possibly

reflecting internal processes, such as deliberation and control. On self vs. neither and self vs. other trials, however, OT only showed a trend on response times (self vs. other: mean difference of 14.78 ms; self vs. neither: 8.72 ms; both $P < 0.13$) (Fig. 3*B*). Finally, on some trials, donors avoided making a decision, opting to wait until the next trial (although they could not predict the subsequent reward options). OT reduced this choice avoidance behavior across all trial types (all $P < 0.05$, Welch two-sample t test) (Fig. 3*C*), perhaps because of overall enhancement in subjective reinforcement.

Inhaled OT thus influenced reward donation decisions by rhesus macaques when there was an option to reward another monkey (other vs. neither and self vs. other, but not self vs. neither). OT enhanced reward donations on other vs. neither trials, but increased selfish behavior on self vs. other trials (Fig. 2). OT-induced changes in attention to the recipient monkey (Fig. 3*A*) and decision time (Fig. 3*B*) were both specific to the donation context (other vs. neither), whereas OT-induced reductions in choice avoidance behavior (Fig. 3*C*) were global.

Discussion

Compared with some other nonhuman primates, social behavior of rhesus monkeys is primarily characterized by competition and aggression, and shows very weak, if any, inclination toward cooperation (36, 37). In a prior study, different levels of endogenous OT were reported in more socially affiliative mother-reared compared with more socially agnostic nursery-reared macaques (38). Here we show that exogenous OT promotes social donation behavior in rhesus macaques, as it does in more egalitarian and monogamous species, like prairie voles and humans. OT-induced prosocial donations were accompanied by enhanced other-oriented attention and decision times. In contrast, in a context in which there was a potential for rewarding self or another monkey, OT slightly increased the tendency for donors to choose selfishly without influencing overt attention and, at most, minimally affecting decision times. The absence of OT-induced enhancement of overt attention on these trials suggests that OT modulates other-oriented preferences through vicarious reinforcement (34). These findings are consistent with context-dependent effects of OT on human social behavior (16, 17, 39) (for a review of human social processing, see ref. 40), implying similar neural mechanisms.

Given the context-specific increase in attention to the other monkey and more deliberative decision latency, it is conceivable that these behaviors are related. Several hypotheses are plausible. On the one hand, OT may increase attention to the other monkey via neural circuits mediating orienting behavior, including amygdala, parietal cortex, and superior colliculus. Increased attention to the recipient may enhance vicarious reinforcement experienced from delivering juice to him. Alternatively, OT may influence neural circuits involved in decision-making, including the striatum and anterior cingulate cortex (see introductory paragraphs). Slowed response times may reflect more deliberate processing of the potential outcomes available (41). A future study designed to probe the temporal evolution of OT-induced effects on attention and decision-making will be needed to resolve these hypotheses.

The direction of OT-induced social enhancement also appears to vary as a function of time. OT initially enhanced self reinforcement but later amplified vicarious reinforcement, although the largest OT-induced effects were prosocial. Although this interaction between time-dependent and context-dependent effects of OT may be specific to our reward allocation task and thus can only be extrapolated with caution, these results suggest that OT may influence self- and other-regarding behaviors via distinct underlying neural mechanisms.

Why might OT promote self reinforcement bias on self vs. other but not on self vs. neither trials? The key difference between the two contexts is the alternative option. In one context, the alternative option has a social consequence (i.e., rewarding the recipient), whereas in the other context, the alternative option does not (i.e., nothing happens to either donor or recipient). OT-induced self reinforcement may depend on the contrast between rewarding self and another individual. We hypothesize that when a decision context presents this contrast, OT can promote selfish behavior. OT influences on self and vicarious reinforcement (16, 17, 39) thus appear to depend on the social state of the underlying neural circuits.

Previous studies in monogamous prairie voles and promiscuous montane voles (*Microtus montanus*) have suggested that mating system may be a key predictor of OT influences on social behavior through the topology of OT receptor localization in neural circuits, mediating reinforcement and motivation (33). A more general difference between prairie voles and montane voles is the frequency and intensity of social interaction (33). Compared with montane voles, prairie voles are biparental, show more selective aggression, and spend more time in close physical proximity (33). Humans and rhesus macaques, too, are highly social mammals; intranasal OT induces prosocial tendencies in humans (15, 16) and, as we now report, in rhesus macaques. These findings suggest that OT may play a critical role in modulating social behavior in highly gregarious mammals, regardless of mating system or parental care strategy.

Intranasal administration of OT in humans has also been shown to increase gaze to the eyes of others (19). We found that OT enhanced gaze directed at the face of the other monkey following active social decision-making but not following passive reward delivery. This finding invites the possibility that OT gates the activity of attention circuits in the brain specifically during active interaction with others. Evidence from human functional neuroimaging studies is consistent with this idea. For example, OT selectively modulates BOLD signal in the anterior cingulate cortex, amygdala, midbrain, and dorsal striatum during a trust game involving other human players, but not during a nonsocial decision-making task (29). Functional connectivity between the amygdala and midbrain structures is also reduced by OT when human participants view emotional faces (28). Finally, OT reduces the subjective evaluation of aversively conditioned faces, and this reduction is accompanied by suppressed BOLD responses in the amygdala and the fusiform gyrus (42).

Consistent with our results, OT modulates deliberation times during social decision-making in humans. For example, OT slows overall evaluation time for rating faces in a nonspecific manner, regardless of whether the images were aversively conditioned or not (42). OT can also speed up decision times; for example, OT decreased overall key press reaction times for evaluating in-group favoritism and out-group derogation in an implicit association test (17).

OT enhanced the frequency of prosocial decisions in the absence of opportunity for direct self reward, but provoked an increase in selfish decisions when choosing between self and other. Such a dual function has also been reported in humans. OT can both promote cooperation and increase out-group bias depending on behavioral context (16, 17, 39). Thus, OT does not appear to have a universal prosocial influence on behavior, but rather amplifies ongoing social information processing (21), perhaps by influencing already existing preferences. It is plausible that OT mediates prosociality and generosity only in an indirect manner. Alternatively, OT may play a more direct and causal role in modulating context-dependent social information processing (e.g., refs. 27–29 for neural evidence), specifically by enhancing the gain of neural circuits mediating vicarious reinforcement and attention.

Recently, OT has been evaluated for potential therapeutic use in clinical conditions attended by dysfunctional social behavior, such as autism spectrum disorders, antisocial personality disorder, and schizophrenia (20–24, 43, 44). Notably, the intranasal nebulization method (35) we developed here is well-tolerated by children for

delivery of other therapeutics (i.e., albuterol), thus opening up avenues for early OT intervention in neuropsychiatric conditions with social deficits. Furthermore, choice-specific effect of OT on increasing other-oriented attention suggests a potential need for active decision-making during OT interventions.

The current finding opens up new opportunities for uncovering the mechanisms underlying the influences of OT on social behavior in a species much more closely related to humans than rodents. Rhesus monkeys have long served as the primary model species for probing the neural mechanisms mediating high-level cognition. Given the strong similarities in social behavior and cognition, and the apparent homologies in underlying neural circuitry, the rhesus macaque provides a powerful model for probing the mechanisms mediating some of the basic behaviors that make complex human social interactions possible.

Methods

General Procedures and Behavioral Task. All procedures were approved by the Duke University Institutional Animal Care and Use Committee. Two donor monkeys (MY and MO) and a recipient monkey (MD) participated in the study. All animals underwent standard surgical procedures for implanting a head-restraint prosthesis at least 6 mo before the present study. The head-restraint prosthesis allowed us to monitor eye position, sampled at 1,000 Hz (SR Research; Eyelink), as well as conduct single-unit recordings in other experiments, not reported here. Both the donor and recipient were head-restrained throughout the experiment. Donors and recipient were unrelated, middle-ranked, and not cage mates. Face of recipient (other; corresponding horizontal and vertical eye positions) was empirically mapped. Rewards were 0.5–1.0 mL of cherry-flavored juice. Within each block, reward size was constant for all three outcomes. A separate solenoid was designated for rewarding neither that only produced clicks but delivered no fluid. To prevent monkeys from forming secondary associations between solenoid clicks and different reward types, all solenoid valves (including the one used to deliver "neither" reward) used to deliver juice rewards were placed in another room. Masking white noise was also played in the experimental room.

Donors began the trial by shifting gaze (± 2.5°) to a central stimulus (0.5° × 0.5°), and maintained fixation (for 200 ms). Choice and cue trials were presented at equal frequencies and randomly interleaved. On choice trials (Fig. 1*B*), two visual targets (4° × 4°) appeared at two random locations of 7° eccentricity and reflected about the vertical meridian. Donors shifted their gaze to one target (± 2.5°) to indicate their choice. On cued trials (Fig. 1*B*), donors maintained fixation while a cue appeared centrally (for 500 ms). On both trial types, the reward onset was followed by a 0 to 0.9 s delay. Donors could freely look around for 0–0.9 s following making a choice and for another 1 s after the reward onset. Data from error trials are not included in analyses.

Data from 12 OT (MY: 5, MO: 7) and 10 saline (MY: 3, MO: 7) sessions were collected on strictly alternating days. Each day session was, on average, 1,274 ± 141 (mean ± SEM) trials. Within each day session, several blocks of the task (a median of 6 and 6.5 blocks for OT and saline, respectively) were completed by the donors. Each of these blocks typically consisted of 192 ± 10 (mean ± SEM) and 205 ± 15 trials for OT and saline, respectively.

Intranasal OT Protocol. Donor monkeys were transported in the primate chair from the colony room to the experimental room. After stabilizing their heads, OT (25 IU/mL; Agrilabs) was delivered via nebulization (Pari Baby Nebulizer) into the nose and mouth continuously for 5 min (5 IU/min) when the donor monkeys were fully awake. On alternating days, nebulized saline served as a control. Before experimental sessions, donor monkeys were first habituated to the nebulizer and then accustomed to saline delivery using the nebulizer in an incremental fashion until they were completely relaxed during the procedure, which typically took about a week. In fact, donor monkeys showed no distress during this procedure. Testing began exactly 30 min after each treatment, at which time a recipient monkey was brought to the experimental setup. In the guinea pig CNS, radioactively labeled OT lasts up to 4 h (45). In humans, intranasal delivery of a similar peptide, vasopressin (differing by only two amino acids), increases its concentration in the CSF after 10 min, and elevated vasopressin levels are maintained for more than 80 min after administration (35). In that study (35), vasopressin levels increased significantly after 30 min. Previous studies in humans have not measured inhaled OT uptake into the CNS. Fig. 1*D* plots CSF OT levels in monkeys 35 min after inhalation, demonstrating efficacy of the intranasal nebulization method (see below). Note that the mask was always pressed very tightly to minimize potential leakage, but nonetheless leakage could have occurred. It is worth noting that CSF OT levels may have continued to increase after the time of CSF measurement, warranting caution in linking absolute CSF OT levels with changes in behavior. Despite these uncertainties, our nebulization technique resulted in a ~2.5-fold increase in CSF OT levels roughly 0.5 h after inhalation.

CSF OT Protocol. To determine whether inhaled OT penetrates the CNS after nebulization, OT concentration in CSF was measured via cervical punctures (on average 35 min after the beginning of inhalation). Cervical punctures were performed by a licensed veterinarian, and targeted the cisterna magna through the juncture between the occipital base and atlas (C1) through the atlanto-occipital membrane. Monkeys were first anesthetized with ketamine (3 mg/kg, i.m.) and dexdomitor (0.075 mg/kg, i.m.). To reverse anesthesia, we administered antisedan (0.075 mg/kg, i.m.) once the animal was returned to its cage after the draw. Approximately 0.5 mL of CSF was drawn using a 24 to 27 gauge needle. At the performing veterinarian's discretion, bupivacaine was administered subcutaneously at the insertion site following needle removal. CSF was immediately frozen on dry ice and sent off-site to be assayed for OT (Biomarkers Core Labs, Yerkes National Primate Research Center, Atlanta, GA) using a commercially prepared kit [Assay Designs (now Enzo Life Sciences); cat. # 900–153: Oxytocin ELISA kit, with very low reactivity with vasopressin]. Samples were assayed "neat" with a range of 15.6–1,000 μL assay volume. This assay has near-zero reactivity with vasopressin, which is chemically similar to OT, thus providing specific quantitation of OT.

Data Analysis. Preference index was a contrast ratio of frequency of choosing an option, n_A or n_B:

$$Preference\ Index = \frac{n_A - n_B}{n_A + n_B}.$$

For choices between self vs. other, n_A and n_B were number of choices to reward other and self, respectively. For choices between other vs. neither, n_A and n_B were number of choices to reward other and neither, respectively. Finally, for choices between self vs. neither, n_A and n_B were number of choices to reward neither and self, respectively. Indices ranged from –1 to 1, with 1 corresponding to always choosing the "prosocial" option to reward the recipient monkey (when that was an option) or to withhold reward from self (self vs. neither). An index of –1 indicated that donors always chose an "antisocial" option to reward self (when that was an option) or to withhold reward from the other monkey (other vs. neither). Preference index of 0 indicated indifference. Frequency of donors looking at recipients was computed from number of gaze shifts to the recipient's facial region (within ± 8.5° spanning from the center of the recipient's face). Reaction times (time from target onset to movement onset) were computed using a 20°/s velocity threshold (46).

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